# THE EIGHTH FREDERICK H. VERHOEFF LECTURE

## PRESENTED BY SAIICHI MISHIMA, MD

# BEHÇET'S DISEASE IN JAPAN: OPHTHALMOLOGIC ASPECTS*

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### INTRODUCTION

BEHÇET'S DISEASE IS ONE OF THE MOST IMPORTANT DISEASES IN OPHTHALMOlogic practice in Japan because of its high incidence and difficulty in its treatment. Since Shikano[1] pointed out that this disease is not rare in Japan, reports on large series of cases appeared, and it was soon discovered that this disease was the most frequent entity in endogenous uveitis.[2] This finding instigated systematic researches, and in 1957 a team organized by Hagiwara[3,4] began to study Behçet's disease and diseases involving mucous membrane, skin, and the eye.

Behçet's disease was envisaged as an independent systemic disease, and research on its genesis and treatment began.[5-9] An increase in the incidence of this disease was recognized in the early 1950s, and attempts were made to conduct an epidemiologic survey in various districts.[10-13] While blindness caused by infectious diseases declined, blindness caused by Behçet's disease increased: by 1965 Behçet's disease was the cause of about 12% of acquired blindness in adults.[14] Thus, this disease became a great concern. The Ministry of Health and Welfare organized the Behçet's Disease Research Committee in 1972, headed by Professor Tamotsu Shimizu,[15] and efforts have been made to conduct a nationwide survey to elucidate its etiology and to find a means of treatment.

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This presentation will attempt to cover ophthalmologic aspects of this disease with particular emphasis on the work carried out in Japan.

## HISTORICAL REVIEW

Before Behçet reported two cases of this disease in 1937, ophthalmologists knew that recurrent hypopyon iritis was associated with various manifestations in the ocular fundus and also in other organs. (The first author to have drawn attention to this appears to have been Reis in 1906, and many case reports appeared in European literature.[25,31,40,68] In Japan, since the report of Ito in 1920, ten case reports had been made before 1940 in ophthalneuroretinitis, retinal angiitis, retinal hemorrhage, and optic atrophy; extraocular symptoms included fever, erythema nodosum, aphthous stomatitis, genital ulcerations, furunculosis, pyodermia, and arthritis. During the 1930s, several reports[16-25] recognized that these systemic manifestations and the recurrent uveitis could be integrated as a new syndrome.

Among others, Behçet[19] reported two cases in 1937 and assembled lesions in the mouth, genital organs, and eye to compose the triple-symptom complex. Furthermore, he claimed to have found elementary bodies in biopsy specimens of tissue from the mouth and genital ulcers, suggesting viral etiology of the disease. In 1940 he compiled an additional four cases, claiming that the so-called triple-symptom complex could be regarded as a disease sui generis.[22] He also described skin lesions, mostly of erythema nodosum-type eruptions, as associated symptoms. Ocular lesions, including not only recurrent iridocyclitis with or without hypopyon but also neuroretinitis as seen today, were also described. This symptom complex was soon identified with the recurrent hypopyon uveitis reported in ophthalmologic literature, and also with the cases reported by Adamantiadès,[16] Dascalopoulos,[17] Whitwell,[18] Weekers and Reginster,[23] Franceschetti and Valerio,[24] and Cavara.[25] The first report to name this symptom complex as "Behçet's syndrome" appears to be that of Jensen,[26] who drew attention to peculiar hyperreactivity of the skin to nonspecific insults, eg, injection of saline solution. In the field of ophthalmology, at least in European languages, Foss[27] was apparently the first author to use the term "Behçet's syndrome," and he reported two cases in 1941.

During the 1940s, many additional cases were reported under various terminologies: Behçet's syndrome,[28-33] Morbus Behçet,[34] iritis récidivante à hypopyon,[35,36] iritis récidivante aphteuse à hypopyon,[37] le syndrome oculo-bucco-genital,[38] grande aphtose or aphtose generalisée,[39] and recurrent aphthous uveitis with mucocutaneous lesions.[40] Extensive reviews of literature were presented,[29,30] and in addition to the three cardinal symptoms of Behçet, ie, recurrence of oral aphthae, genital ulcerations,

and ocular involvements in the form of iridocyclitis and neuroretinitis, new additional symptoms were recognized: skin lesions including erythema nodosum-like, acne-form, and papulo-pustular eruptions, nonspecific hyperreactivity of the skin, hydrops of the knees, epididymitis, and gastrointestinal and neurologic symptoms.[29] Thromboangiitides of the retina and of the extremities were also regarded as important associated symptoms.[36,38]

In dermatologic literature, aphthous stomatitis and associated diseases were discussed in connection with Behçet's syndrome.[39,41] Furthermore, differentiation of Behçet's syndrome from other disorders affecting the skin, mucous membranes, and the eye was in dispute: these disorders were dermatostomatitis of Baader, aphthosis acuta of Neumann, erythema exudativum of Hebra, ulcus vulvae acutum of Lipschütz, ectodermose érosive pluriorificielle of Rendu-Fiessinger, Stevens-Johnson disease and Reiter's disease. It was discussed[42] that the dermatostomatitis, ectodermose érosive pluriorificielle, and Stevens-Johnson disease belong to the identical syndrome as the case first reported by Fuchs[43] as herpes iris conjunctivae. They were grouped in the acute mucocutaneo-ocular syndrome of Fuchs. The Behçet's triple-symptom complex was identified as the iridocyclitis septica of Gilbert,[44] and it was grouped in the recurrent mucocutaneo-ocular syndrome of Gilbert.

On the other hand, some authors[45-47] believed that Behçet's syndrome, ectodermose érosive pluriorificielle, and other mucocutaneo-ocular affections are related and that distinct delineation of syndromes is not possible. Frequent association of other systemic symptoms with the three cardinal symptoms of Behçet became known, and it was recognized that a long period is needed for the appearance of all three cardinal symptoms. This led to a discussion that the criteria of the triple-symptom complex should be reconsidered and that cases lacking a complete set of three symptoms should also be included in the Behçet's syndrome.[31] This opinion was later supported but appeared to have caused confusion in differentiating this syndrome from other diseases involving skin, mucous membrane, and the eye.

Consequently, the diseases enumerated previously were grouped simply as the mucocutaneo-ocular syndromes;[48] use of this general term to include Behçet's syndrome[49] found some support. Haensch[50] included Behçet's syndrome in the chronic recurrent aphthosis and believed it to be the severe form of aphthosis. Schreck[51] classified the diseases affecting the mucous membrane, skin, and the eye into three groups: (1) the cutaneomuco-oculoepithelial syndrome, which is subdivided into (*a*) syndroma cutaneomuco-oculoepitheliale erythematicum Fuchs, which in-

cluded dermatostomatitis of Baader, ectodermose érosive pluriorificielle, and Stevens-Johnson disease, (*b*) syndroma cutaneomuco-oculoepitheliale bullosum, including pemphigus, (*c*) syndroma cutaneomuco-oculoepitheliale allergicum, and (*d*) syndroma cutaneomuco-oculoepitheliale hereditarium; (2) syndroma cutaneomuco-uveale, which included Behçet's syndrome; and (3) syndroma urethro-conjunctivo-articulare, which is Reiter's disease.

In spite of the confusion regarding the classification and terminology, accumulation of case reports of Behçet's syndrome continued.[52-54] France et al[55] reviewed 33 cases in 1951, and the symptoms of the eye, skin, mucous membrane, thrombophlebitis, joints, fever, leucocytosis, and CNS involvement were analyzed. Histopathologic studies pointed out that inflammatory reactions involving small vessels underlie manifestations in various organs. Sezer[56,57] examined 23 cases and maintained that this syndrome is a disease entity, claiming that virus was isolated from the patients' material.

With this historical background, Hagiwara[3,4] organized a research team consisting of various specialists to study the mucocutaneo-ocular syndromes. They compiled more than 200 cases of Behçet's syndrome and concluded through long-term observations that the mucocutaneo-ocular syndromes reported previously be grouped into three categories: (1) erythema exudativum multiforme syndrome, which includes erythema exudativum of Hebra, ectodermose érosive pluriorificielle of Rendu-Fiessinger, Stevens-Johnson disease, and dermatostomatitis of Baader; (2) Behçet's syndrome, which includes Behçet's syndrome, Franceschetti-Valerio syndrome, ulcus vulvae acutum of Lipschütz, chronic recurrent aphthosis of Kumer, and acute aphthosis of Neumann; and (3) Reiter's disease. Furthermore, Behçet's syndrome was envisaged as an independent systemic disease affecting various organs including the skin, mucous membrane, and the eye. Through an extensive review of literature, Mavioğlu[58] discussed that this symptom complex be understood as Behçet's recurrent disease, indicating its nature as an independent systemic disease entity. During the course of studies headed by Hagiwara, the importance of skin lesions in the diagnosis of Behçet's disease was stressed by Urayama,[59,60] Furusawa,[61] Asaoka,[62] and Nishiyama,[63] who included them among the cardinal symptoms on which diagnosis of this disease is based. Four cardinal symptoms, as well as other associated symptoms, evolved as criteria of diagnosis: ocular changes, aphthous ulcer of the oral mucous membrane, genital ulcerations, and skin lesions. Since the disease appears as recurrent attacks and requires a long period to show all four cardinal symptoms, ie, the "complete type" of the disease, cases lacking

one of the cardinal symptoms were included in Behçet's disease, and the term "incomplete type" was given.

For neurologic complications, Cavara and D'Ermo[64] proposed the term "Neuro-Behçet's syndrome." By the same token, cardiovascular complications were called "Cardio-Behçet's syndrome" by Urayama,[59] and "Vasculo-Behçet's syndrome" by Shimizu.[65] Tsukada et al[66] called the intestinal complications "intestinal-Behçet's syndrome." These terms are used by many investigators.

At the international symposium on Behçet's disease held in 1966, comprehensive compilation of previous publications was made and an agreement was reached that the syndrome be called "Behçet's disease," since it is an independent systemic disease.[67] Bietti and Bruna[68] presented an extensive review on the ophthalmologic aspects and showed a geographic distribution of this disease, indicating high incidence in Japan and Mediterranean countries.

## DIAGNOSTIC CRITERIA

Although Behçet[19] claimed its viral etiology, this has not been proved and the etiology of this disease still remains unknown. The diagnosis must, therefore, be made on the basis of a combination of clinical symptoms. The concept of four cardinal symptoms and other associated symptoms, as described in the preceding section, has been adopted. Common clinical features of these symptoms is that they appear singly or in association as attacks that recur often over a long period with the same or different combinations of symptoms. The oral aphtha is the initial symptom in 50% to 70% of the patients,[3,4,61-63,69-71] followed by skin and ocular symptoms. In about 20% of patients, the ocular attacks occur as the initial manifestation alone or together with other symptoms.[61,62,70] According to Furusawa,[61] the time elapsed until the complete set of the cardinal symptoms appeared was less than one year in 28%, less than two years in about 28%, five years in about 28%, and longer than five years in about 12%; in some cases it took even ten years. This long time-course constitutes a problem in diagnosis when one sees a patient exhibiting only some of the cardinal symptoms. Thus the concept of the "complete type" and the "incomplete type" was introduced. In addition, even when only one cardinal symptom is present, long-term follow-up is necessary. For example, Kohno and Nakano[72] reported that in about 45% of patients who initially consulted with oral aphthae, other cardinal symptoms developed in the course of years. For this reason, "suspect type" and "possible type" were classified, although they are not regarded as Behçet's disease.

In the skin lesions, erythema nodosum-like lesions, folliculitis or acne-like lesions, and thrombophlebitis were included. Cutaneous hypersen-

sitivity originally described by Jensen[26] was also considered characteristic[71,73] and was included in the skin lesions. On the basis of the previously described diagnostic criteria, many works on Behçet's disease had been done before 1970.

When the Behçet's Disease Research Committee was organized in 1972, it was thought that unified diagnostic criteria of the disease was necessary to conduct further cooperative works among various specialists. Thus, the members of the clinical research section of the Committee conferred and made the following guide for diagnosis to be distributed throughout Japan:[74]

GUIDE TO DIAGNOSIS OF BEHÇET'S DISEASE

Since the cause of Behçet's disease is unknown, it is diagnosed through a combination of clinical symptoms which are classified under major and minor diagnostic criteria. Behçet's disease itself is divided into complete and incomplete types. However, owing to the chronic course of its development, suspect and possible types are included in order that early symptoms are not overlooked.

I. THE SYMPTOMS

The main symptoms of Behçet's disease are manifested in the oral mucous membrane, skin, the eye, and the external genital region. It may involve joints, intestine, epididymis, the vascular system, and the CNS. Individual symptoms show recurrences and follow a chronic course. The symptoms comprising the major and minor criteria are described below.

*1. Major criteria*

A. Recurrent aphthous ulceration of the oral mucous membrane

Painful round or oval ulcers, usually small and sharply defined, are found in the labial, buccal, gingival, and lingual mucous membranes. The ulcers usually heal in 7 to 10 days without recognizable scarring, but they do show recurrences.

B. Skin lesions

a. Erythema nodosum-like lesions: Tender red nodes, slightly raised above the skin level, appear repeatedly on the anterior surface of the legs; they may, however, occur elsewhere. They involute usually within a few weeks without developing ulcers.

b. Thrombophlebitis: Painful subcutaneous strands and nodules are found along cutaneous veins usually in the extremities. The condition may also be seen after injection or blood sampling.

c. Folliculitis or acne-like lesions: Numerous papules and pustules appear on the face, neck, back, and extremities.

d. Cutaneous hypersensitivity: Papules are also seen after pricking with a needle or shaving; small pustules may appear.

C. Ocular symptoms

a. Iridocyclitis

1. Recurrent hypopyon iritis is typical, usually disappearing within several days.

2. In many cases, serous iritis may be seen without developing hypopyon iritis. In remission, posterior synechia, iris atrophy, and/or keratic precipitates showing previous iritis may be found.

b. Chorioretinitis: Typical retinitis consists of edematous opacification of the retina, macular exudates, hemorrhages, and retinal angiitis. Vitreous opacities caused by exudates are present. Attacks of exacerbation often recur. (a and b may coexist, but may be found independently.)

c. Sequelae of a and b: Diffuse retinal atrophy, optic nerve atrophy, complicated cataract, secondary glaucoma, and phthisis.

D. Genital ulcers

Painful punched out ulcers are seen usually in the scrotum or vulva. They heal with scarring in many cases.

2. *Minor criteria*

A. Arthritis: Painful swelling with redness resembling rheumatoid arthritis appears in large joints, eg, knee, foot, hand, and elbow. It is transient and recurrent. Unlike rheumatoid arthritis, roentgen ray examination shows no or very little change in the bone or cartilage. Rheumatoid arthritis test is negative.

B. Intestine: Multiple ulcers occur in the ileo-coecal region; the symptoms suggesting ulceration are appendicitis-like abdominal pain, diarrhea, and hemorrhages.

C. Epididymitis: A transient haphalgesic swelling may occur.

D. Vascular symptoms: Obliterating thrombophlebitis, arterial occlusion, and aneurysm may be seen.

E. Neuropsychiatric symptoms: Multiple neurologic disorders, eg, pyramidal, extrapyramidal, cranial nerve symptoms, etc, and psychiatric symptoms may appear.

3. *Examination*

Prick test: After pricking the skin with a sterile needle, a red papule may occur in 24 to 48 hours and a pustule may appear at the center.

II. DIAGNOSIS

A. Complete type: The four main symptoms appear simultaneously or at different times during the clinical course.

B. Incomplete type:

a. Three main symptoms appear simultaneously or at different times during the clinical course.

b. Recurrent hypopyon iritis or typical retinitis is present accompanied by one of the other main symptoms.

C. Suspect type: Two main symptoms appear simultaneously or at different times.

D. Possible type: One main symptom appears during the clinical course.

NOTE 1: In suspect and possible types, there is a possibility of the late appearance of other main symptoms and therefore follow-up treatment is required.

NOTE 2. In complete and incomplete types of Behçet's disease, central nerve symptoms may appear and become of concern; this is called the neuro-Behçet's syndrome.

## FREQUENCIES AND ASSOCIATION OF SYMPTOMS

On the basis of this criteria, a nationwide survey of patients was conducted in 1972 under the direction of Yamamoto. By the secondary survey,[75] a total of 2,031 patients, 928 complete and 1,103 incomplete types, were compiled and their symptoms were analyzed. The number of patients manifesting the symptoms of the major criteria is listed in Table I. Oral aphthae was the most frequent, appearing in 98.3%, followed by skin lesions, 90.4%, genital ulcers, 79.8%, and the ocular symptoms, 78.6%. The prick test was carried out in a total of 1,060 patients and positive results were obtained in 841 cases, ie, 79.3%; this figure is in agreement with the results of Urayama et al[71] and Matsubara et al.[73] The results on symptoms of minor criteria are shown in Table II. Arthritis was the most frequent, seen in 60% of cases, followed by intestinal symptoms, seen in 27%. Cardiovascular and neurologic symptoms were seen in about 8%. The incidences of various symptoms of this disease were analyzed previously for small samples,[55,58,60,62,71,76-79] and the figures are in agreement with the present results.

A factor analysis[75] to examine association of various symptoms (Fig 1) revealed high association among symptoms of the major criteria, confirming the concept of four cardinal symptoms. Close association of the skin hypersensitivity to prick test with other major criteria symptoms confirms the importance of this test for diagnosis. Frequent association of arthritis had been noted by many authors,[55,57,58] but its classification to minor criteria is justified, since its association with other major criteria symptoms is less than the association among the major criteria.

Since the genital ulceration in males usually occurs on the scrotum and penis, it is considered skin lesions.[79] In females, ulcers on labia majora and minor may be regarded as skin lesions and ulcers in the vagina are mucosal manifestations. Thus, the cardinal manifestations were classified by Firat[79]

TABLE I: NUMBER OF CASES MANIFESTING SYMPTOMS OF MAJOR CRITERIA IN MALE AND FEMALE PATIENTS*

| MAJOR CRITERIA | MALE | | FEMALE | | TOTAL | | |
|---|---|---|---|---|---|---|---|
| | NO. CASES WITH SYMPTOM (%) | TOTAL NO. OF CASES ANALYSED | NO. CASES WITH SYMPTOM (%) | TOTAL NO. OF CASES ANALYSED | NO. CASES WITH SYMPTOM (%) | TOTAL NO. OF CASES ANALYSED | $\chi_2$ VALUE FOR SEX DIFFERENCE |
| Aphtha | 1,130 (97.9) | 1,154 | 850 (98.8) | 860 | 1,980 (98.3) | 2,014 | 2.50 |
| a) Erythema nodosum | 815 (75.2) | 1,084 | 681 (82.5) | 825 | 1,496 (78.4) | 1,909 | 14.97† |
| b) Thrombophlebitis | 316 (33.5) | 944 | 159 (24.1) | 659 | 475 (29.6) | 1,603 | 16.26† |
| c) hypersensitivity | 689 (69.0) | 998 | 451 (63.6) | 709 | 1,140 (66.8) | 1,707 | 5.50‡ |
| a) and/or b) and/or c) | 1,017 (89.8) | 1,132 | 772 (91.3) | 846 | 1,789 (90.4) | 1,978 | 1.12 |
| Ocular symptoms | 997 (86.2) | 1,156 | 561 (67.8) | 827 | 1,558 (78.6) | 1,983 | 97.04† |
| Genital ulcers | 853 (76.8) | 1,111 | 684 (83.8) | 816 | 1,537 (79.8) | 1,927 | 14.47† |

*From Masuda et al.[75]
†$P < 0.01$.
‡$P < 0.05$.

TABLE II: NUMBER OF CASES MANIFESTING SYMPTOMS OF MINOR CRITERIA IN MALE AND FEMALE PATIENTS*

| | | MALE | | FEMALE | | TOTAL | | |
|---|---|---|---|---|---|---|---|---|
| | MINOR CRITERIA | NO. CASES WITH SYMPTOM (%) | TOTAL NO. OF CASES ANALYSED | NO. CASES WITH SYMPTOM (%) | TOTAL NO. OF CASES ANALYSED | NO. CASES WITH SYMPTOM (%) | TOTAL NO. OF CASES ANALYSED | $\chi_1$ VALUE FOR SEX DIFFERENCE |
| | Arthritis | 599 (56.1) | 1,067 | 497 (62.6) | 794 | 1,096 (58.9) | 1,861 | 7.84† |
| | Intestinal symptoms | 283 (27.7) | 1,023 | 197 (25.9) | 762 | 480 (26.9) | 1,785 | 0.73 |
| | Vascular symptoms | 86 (8.7) | 989 | 47 (6.3) | 742 | 133 (7.7) | 1,731 | 3.33 |
| Neuro-Psychiatric symptoms | a) Pyramidal symptoms | 104 (9.8) | 1,066 | 50 (6.3) | 791 | 154 (8.3) | 1,857 | 7.04† |
| | b) Cranial nerve symptoms | 83 (7.8) | 1,057 | 49 (6.2) | 788 | 132 (7.1) | 1,845 | 1.81 |
| | c) Psychiatric symptoms | 109 (10.3) | 1,057 | 50 (6.4) | 781 | 159 (8.6) | 1,838 | 8.69† |
| | a) and/or b) and/or | 160 (14.8) | 1,079 | 97 (12.2) | 797 | 257 (13.7) | 1,876 | 2.74 |

*From Masuda et al.[75]
†$P < 0.05$.

into three categories: (1) mucosal manifestations including aphthous lesions, vaginal ulcers, and gastrointestinal and pulmonary disturbance, (2) ocular involvement, and (3) skin lesions. Other symptoms such as vascular episodes, joint manifestations and CNS involvements were classified as secondary manifestations. Similar grouping was also adopted by Furusawa.[61] Although this grouping of the cardinal symptoms appears to be logical, gastrointestinal and pulmonary symptoms must be excluded from the cardinal symptoms from the diagnostic point of view, since they occur rarely and their associations with other cardinal symptoms are low (Fig 1).

The initial manifestations of this disease can be manifold. Occasionally general weakness, low-grade fever, or sore throat may precede appearance of cardinal symptoms.[77] Many authors agree that, among the cardinal symptoms, oral aphtha is the initial manifestation in the majority of cases. Imai[70] analyzed, in 209 cases, 139 males and 70 females, the incidences of the cardinal symptoms being the initial manifestation of the disease. Sometimes a single symptom appeared initially, but sometimes more than two symptoms appeared almost simultaneously, ie, within a month interval, and the combination of symptoms was manifold. The incidences of the initial symptoms are shown in Table III. The oral aphtha was by far the most frequent manifestation, appearing initially in about 60% of the male and in

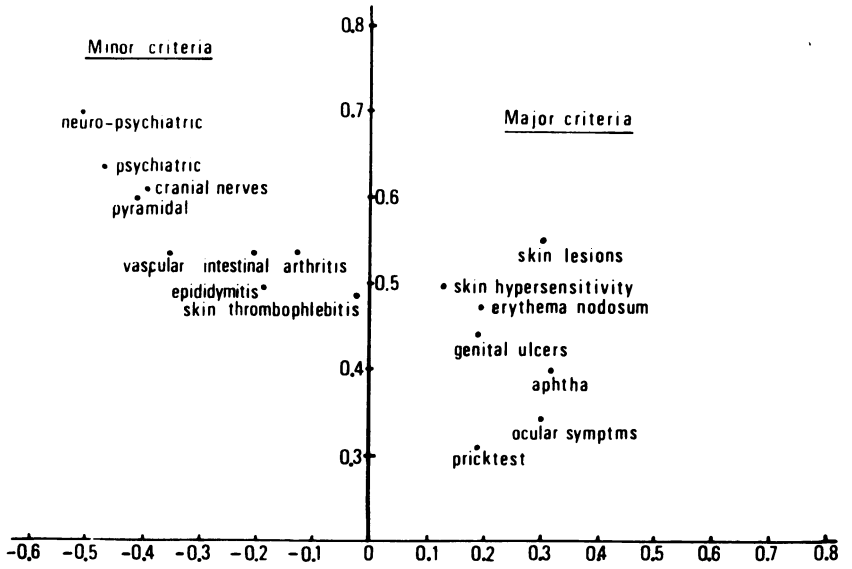


FIGURE 1
Factor analysis on association of clinical symptoms. Closer distance between symptoms indicates higher association. Ordinate and abscissa are in arbitrary units (from Masuda et al[75]).

TABLE III: INCIDENCE OF MAJOR CRITERIA SYMPTOMS BEING INITIAL MANIFESTATIONS*

| | MALES (139 CASES) | FEMALES (70 CASES) | TOTAL (209 CASES) |
|---|---|---|---|
| Ocular symptoms | 35 (25.4)† | 6 (8.6) | 41 (19.7) |
| Oral aphtha | 82 (59.4) | 59 (84.3) | 141 (67.8) |
| Genital ulcer | 20 (14.5) | 18 (25.7) | 38 (18.3) |
| Cutaneous hypersensitivity | 39 (28.3) | 18 (25.7) | 57 (27.4) |
| Erythema nodosum | 19 (13.8) | 6 (8.6) | 25 (12.0) |

*From Imai.[70]
†No. of cases (percent).

84% of the female patients. The incidence of the ocular symptoms being the initial manifestation was higher in male (25.4%) than in female (8.6%) patients. The time interval between the appearance of the initial symptom and the other cardinal symptoms is also variable. The averages of the time intervals are shown in Table IV. The average order of appearance of the cardinal symptoms is as follows: oral aphtha, erythema nodosum-like lesions, skin hypersensitivity, ocular symptoms, and genital ulceration in males, and oral aphtha, skin hypersensitivity, genital ulceration, erythema nodosum, and ocular lesions in females. These data confirm the opinions of many authors regarding the order of appearance of the major symptoms of this disease.

## STATISTICS AND EPIDEMIOLOGIC SURVEY

### BEHÇET'S DISEASE IN ENDOGENOUS UVEITIS

At the Department of Ophthalmology of Tokyo University, statistics on the causes of endogenous uveitis have been compiled every year, and Behçet's disease was found to comprise the leading cause of endogenous uveitis.[2,80-

TABLE IV: AVERAGE TIME INTERVAL (YEARS) OF ONSET AFTER INITIAL MANIFESTATIONS*

| | MALES | FEMALES | AVERAGE FOR TOTAL |
|---|---|---|---|
| Ocular symptoms | 2.43 | 2.98 | 2.60 |
| Oral aphtha | 0.85 | 0.28 | 0.66 |
| Genital ulcer | 3.03 | 2.45 | 2.83 |
| Cutaneous hypersensitivity | 1.94 | 2.07 | 1.96 |
| Erythema nodosum | 1.87 | 2.87 | 2.23 |
| Fever | 2.08 | 1.68 | 1.98 |
| Arthritis | 2.24 | 2.71 | 2.40 |

*From Imai.[70]

TABLE V: CAUSES OF ENDOGENOUS UVEITIS FROM 1965 TO 1977 AT THE DEPARTMENT OF OPHTHALMOLOGY OF TOKYO UNIVERSITY

| | 1965-1969* | | 1970-1973† | | 1974-1977‡ | |
|---|---|---|---|---|---|---|
| | NO. OF PATIENTS | (%) | NO. OF PATIENTS | (%) | NO. OF PATIENTS | (%) |
| Behçet | 256 | (24.8) | 348 | (32.0) | 193 | (23.2) |
| Vogt-Koyanagi-Harada | 70 | (6.8) | 106 | (9.7) | 82 | (9.9) |
| Sarcoidosis | 35 | (3.4) | 62 | (5.7) | 66 | (7.9) |
| Toxoplasmosis | 126 | (12.2) | 77 | (7.1) | 38 | (4.6) |
| Tuberculosis | 22 | (2.1) | 45 | (4.1) | 25 | (3.0) |
| Glaucomato-cyclitic crisis | 46 | (4.5) | 57 | (5.2) | 59 | (7.1) |
| Others | 476 | (46.2) | 394 | (36.2) | 369 | (44.4) |
| Total No. of uveitis | 1,031 | | 1,089 | | 832 | |
| Total No. of out-patients | 51,128 | | 34,859 | | 33,951 | |

*From Araki.[83]
†From Nakae et al.[84]
‡From Namba et al.[98]

[84] Such statistics from the last 12 years are shown in Table V. Behçet's disease was seen in more than 20%. Other major causes of endogenous uveitis are Vogt-Koyanagi-Harada disease, sarcoidosis, toxoplasmosis, glaucomatocyclitic crisis, and tuberculosis. In about 44% the causes could not be determined. The trend of the incidence of Behçet's disease in uveitis since 1954 is illustrated in Fig 2. From 1954 to 1958 the incidence increased, and this was attributed to an increase of this disease rather than to increased interest in the disease, in view of a sharp increase in the blindness caused by Behçet's disease[14]; this will be discussed following. From 1959 to the present, the incidence of the Behçet's disease has remained high. Similar statistics carried out at Tohoku University,[60,70,85] Hokkaido University,[86] and Kyushu University[87] gave similar figures, indicating that our statistics are representative of the national trend.

These results are different from the statistics of the uveitis clinic of California University, San Francisco,[86] or those in England,[88] where Behçet's disease is rare.

## EPIDEMIOLOGIC SURVEY

The nationwide survey was made possible by the Behçet's Disease Research Committee: a total of 4,132 patients, including suspect and possible types, were reported in 1972 from hospitals throughout the country, with the exception of Okinawa, and they were analyzed by Yamamoto et al.[89]

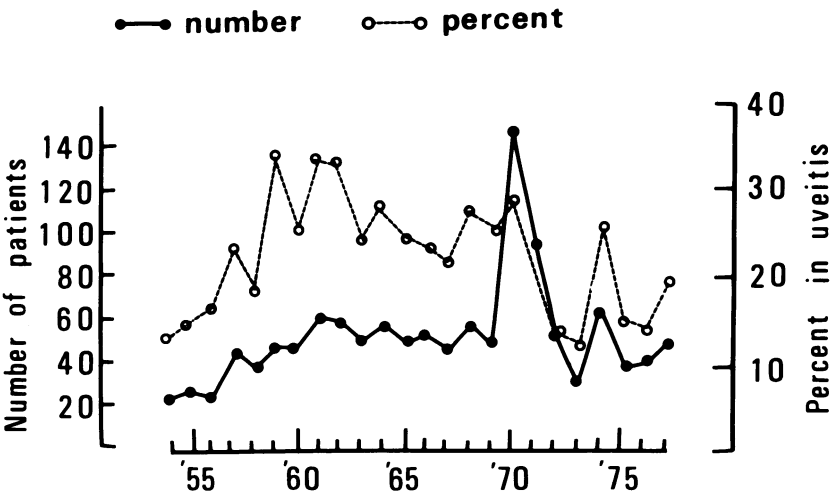


FIGURE 2
Number of patients with Behçet's disease and percentage in endogenous uveitis, from 1954 to 1977, at Department of Ophthalmology of Tokyo University. Abscissa shows years.

From the primary survey, the prevalence rates of this disease were calculated for various districts (Fig 3). Prevalence rates were high in the northern districts and lower in the southern districts. The overall prevalence rate was estimated to be 7 to 8.5 per 100,000 population, considering hospitals and clinics that did not make reports in the survey. Consequently, the total number of patients in the country would be 7,000 to 8,500. Results of the epidemiologic survey[10-13] previously carried out in some districts agreed fairly well with these results. A later survey in Okinawa[90] gave a prevalence rate of 11.6 per 1,000,000 population.

By the secondary survey, 2,520 persons were included; there were 928 complete types and 1,103 incomplete types of Behçet's disease, 326 suspect and 149 possible types, and 14 patients with an unknown type. The male patients were more numerous than the female patients, and the male-female ratio was 1.73 in the complete type and 1.09 in the incomplete type. Among the major criteria symptoms, the ocular symptoms were more frequently seen in male (86.2%) than in female (67.8%) patients. Erythema nodosum and genital ulcers were more frequent in females than in males, whereas thrombophlebitis occurred more often in males than in females (Table I). Among the minor criteria symptoms, arthritis was slightly more frequent in females than in males, but severe vascular and neurologic symptoms occurred more often in males than in females (Table II).

The age distribution of patients at the time of onset is shown in Fig 4. The

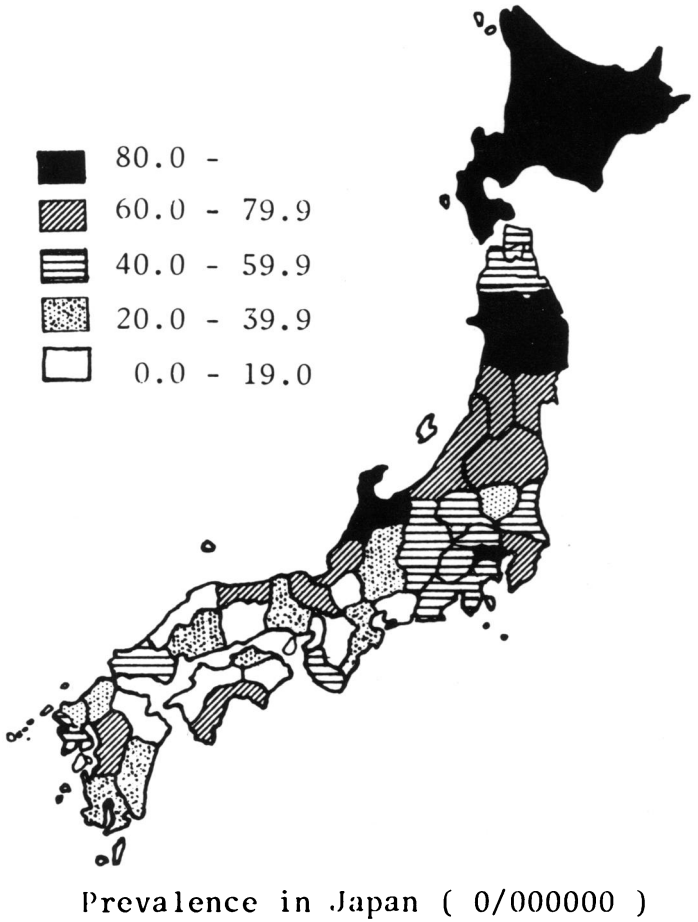


FIGURE 3
Prevalence rate of Behçet's disease in various prefectures in Japan. Numbers are prevalence rates per million population (from Yamamoto et al[89]).

peak age was between 20 to 34 years in males and 30 to 44 years in females. This age distribution is in agreement with the distribution calculated previously in a smaller number of patients.[55,58,62,70,71,76,78] Familial occurrence was found in 46 patients, or about 2%; this agrees with figures reported for Hokkaido,[11] Kyushu,[12] and Akita[13] districts by previous surveys. The patients' occupations were compared with the national occupation survey of the year 1970; patients were found in significantly higher incidence among transportation-communication groups than in the general population. There were many cardrivers among them. A survey in the

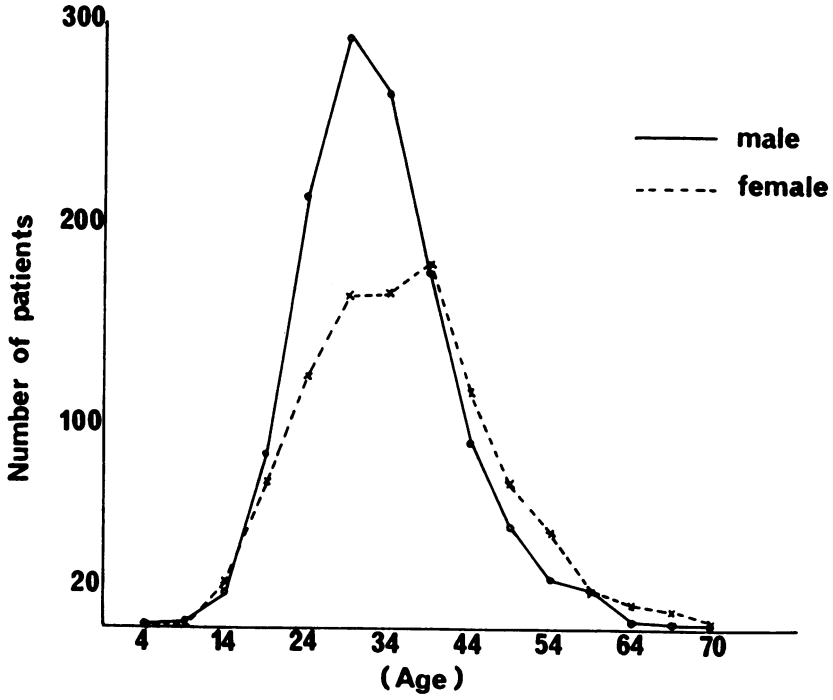


FIGURE 4
Age distribution at time of onset in male and female patients (from Yamamoto et al[89]).

Osaka area[91] showed, however, that the incidence rate in the transportation group did not correlate significantly with the daily time of work or with period of work before onset. No definite relation was found between the incidence and drugs that had been previously taken by the patients.

Since the incidence of this disease is particularly high in Japan, the survey was extended to the Japanese population living elsewhere and to people living close to Japan. A survey was made in Hawaii on various ethnic groups,[92] but no single case was found in the Japanese population; at least 15 patients should have been found if the prevalence rate in Japan was to apply. Thus, it is possible that some environmental factors play a role in the chain of events leading to manifestation of this disease. A survey performed in Taiwan[14] indicated that this disease is much less frequent there than in Japan.

## CLINICAL COURSE OF PATIENTS

In the secondary survey,[75] it was found that deterioration over the status in the preceding year occurred at higher incidence in the complete type than

in the incomplete type. Among the major criteria symptoms, those who had ocular symptoms, genital ulcers, thrombophlebitis, and skin hypersensitivity showed a higher rate of deterioration than those without these symptoms. Rate of deterioration was high in patients with ocular symptoms, since the ocular changes show unfavorable prognosis; the rate of progression is higher in males (45.4%) than in females (22.9%). Among the minor criteria symptoms, those who had vascular and neuropsychiatric symptoms showed a higher rate of deterioration than those without these symptoms.

Eighteen patients died among a total of 2,031 patients with Behçet's disease in the national survey.[89] An analysis of 281 patients who died between July 1972 and May 1976 revealed that the male to female ratio was 2.02.[93] The peak age of death was in the 40s, and the average age was 43.5 years in men and 48.9 years in women. Intestinal, cardiovascular, pulmonary, and neurologic involvements were frequent causes of death.

### BEHÇET'S DISEASE IN ACQUIRED BLINDNESS

A survey in 1965 gave a figure of about 210,000 acquired blindness cases throughout the country, and approximately 65% of them were caused by acquired diseases.[14] There are five national centers for the blind in the country. In 1965, blindness in 5% (39 of 746) of the patients admitted to the centers was caused by Behçet's disease, but this increased to 11.8% (104 of 377 admitted cases) in 1970. At the National Center for the Blind in Tokyo, the incidence of Behçet's disease recorded also increased from 6.4% in 1959 to 16.7% in 1969. Accordingly, assuming that the figure of 1965 is applicable and 12% of acquired blindness in Japan is caused by Behçet's disease, 16,000 people today would have blindness caused by Behçet's disease.[14]

### OCULAR SYMPTOMATOLOGY

The symptoms of Behçet's disease recur in various organs, and the extraocular symptomatology has been described repeatedly in many reviews.[55,58,76-79,94-96] In this section, therefore, description will be concentrated on the ocular symptomatology. The ocular affections show poor prognosis and are the most serious of affections in Behçet's disease, excluding the CNS and cardiovascular involvements, which are life-threatening.

In a large series of patients, the rates of ocular affections were shown to be 83% to 95% in males and 67% to 73% in females[70,71,75,87] (Table I). The ocular involvements are much more frequent in males than in females; the male to female ratio of involvement is 1.78 (Table I). Furthermore, it will

be shown that the prognosis of the ocular changes is more unfavorable in males than in females. The ocular symptoms usually appear subsequent to the oral apthae and skin lesions. The average time elapsed after the initial manifestation of the disease, which is often oral aphtha, until the ocular lesions appeared is about 2.4 years in males and 3.9 years in females (Table IV). However, in about 20% of cases the ocular lesions can be the initial symptoms,[61,70] ie, 25.4% in males and 8.6% in females (Table III). Usually both eyes are affected: this occurs in about 83% to 93% of the cases with ocular lesions.[61,70] The peak age in the distribution of the onset of the ocular symptoms is between 20 and 34 years in men and 30 and 40 years in women.[70]

## SYMPTOMS

### *Iridocyclitis*

The classic form of iridocyclitis in Behçet's disease is the recurrent hypopyon iritis (Fig 5). Even if hypopyon is not detectable by slit-lamp biomicroscopy, it may be found in the lower chamber angle by gonioscopy; this may be called the angle hypopyon. A characteristic feature of hypopyon in this disease is that it is not sticky and it moves by gravity when the patient

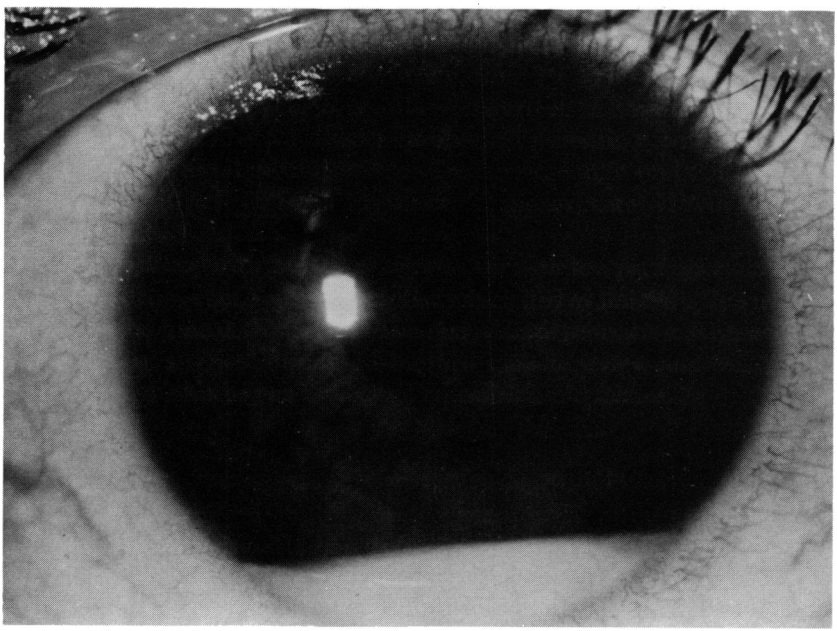

FIGURE 5
Typical hypopyon iritis.

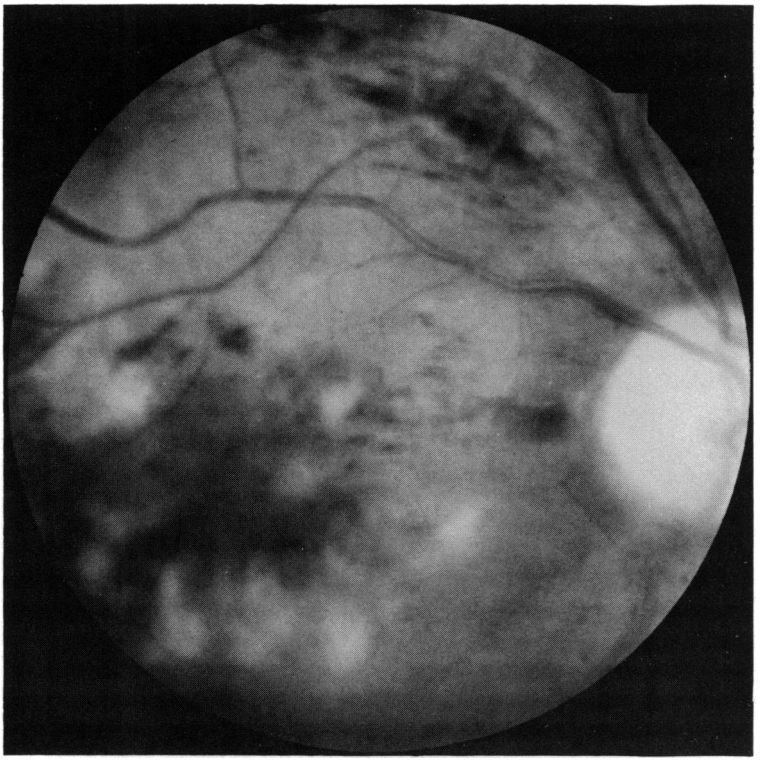

FIGURE 6
Example of fundus-type attack in 29-year-old man. Intense retinal edema, yellowish-white exudate, and hemorrahges are seen in macular region.

keeps a changed head position for several minutes. The hypopyon usually disappears in several days without leaving much tissue damage. At the beginning of the attack, the cellular constituents of hypopyon are almost exclusively neutrophil polymorphonuclear leucocytes, without much sign of leucocytoclasis.[97] Only at the later stage do lymphocytes appear.

It is well known that hypopyon is not always present and the anterior segment involvement takes a form of serous iridocyclitis; pericorneal injection, aqueous flare, fine aqueous floaters, and keratic precipitates are seen. Detailed analysis[98] of clinical symptoms was carried out in 38 cases for a period ranging from 1.3 to 8 years, with the average period of three years. A total of 180 attacks were recorded. Serous iridocyclitis was seen in 68.4% and hypopyon was seen in 31.6%; angle hypopyon was found in 19.4% and hypopyon was detectable with slit lamp only in 12.2%. Opacity in the anterior vitreous cavity is also found frequently.

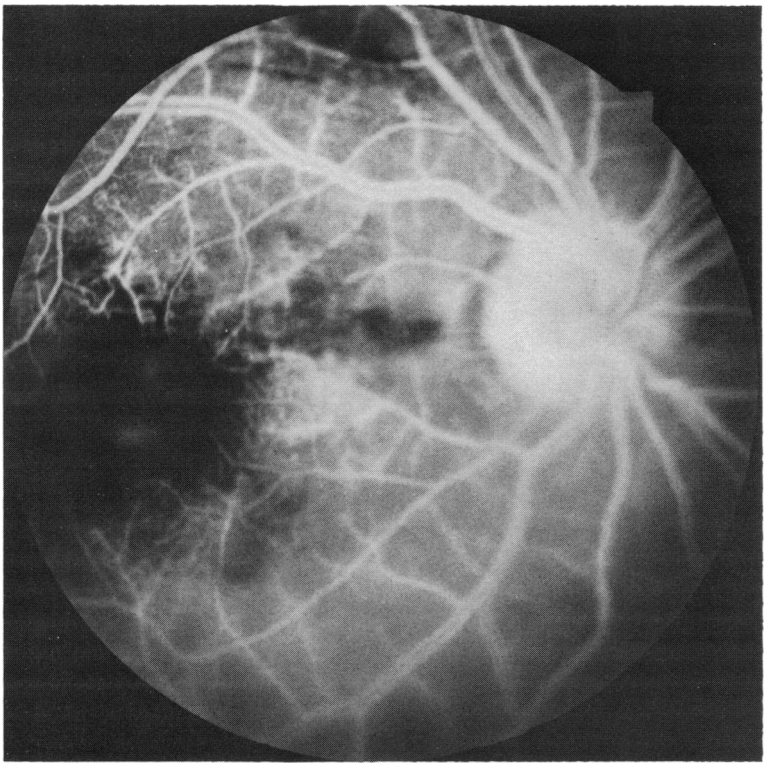

FIGURE 7
Fluorescein angiography of fundus shown in Fig 6, at 21 seconds after injection. Perimacular vascular obliteration and diffuse dye leakage from vessels around area are seen.

Posterior synechia, iris atrophy, and peripheral anterior synechia develop during the course of repeated attacks. The posterior and peripheral anterior synechiae are the main causes of secondary glaucoma. On rare occasions hyphema may appear.[99]

*Fundus changes*

The fundus changes in Behçet's disease have been described by many authors, and they may be summarized, according to Hagiwara[3] and Furusawa,[61] as follows: During the acute attack, hyperemia and edema of the optic disc, venous engorgement, intense retinal edema, yellowish-white exudates, and retinal hemorrhages resembling venous occlusion are seen (Fig 6). Sometimes white sheathing of the vein can also be seen. The exudative and hemorrhagic changes are often found in the posterior pole region, but they may be seen also in the peripheral area. Involvement of

the macular area is most often found, in about 36%[61] of cases. In attacks of slight degree, hyperemia of the optic disc, venous engorgement, capillary dilatation, and retinal edema, usually in the posterior pole region, may be the only findings. During remission, slight hyperemia of the optic disc, venous tortuosities, capillary dilatation, retinal edema, and opacity are seen. Retinal edema is most often seen in the macular area, which shows after repeated attacks degenerative changes with irregular surface and mottled and microcystic appearance. Macular hole may also develop. The retinal arteries and veins may develop sclerotic changes, and after repeated attacks, complete obstruction of the retinal artery and optic atrophy may result. Retinal neovascularization, vitreous hemorrhage, and consequent proliferative changes in the vitreous are also found. In severe cases, total detachment of the retina may occur and degenerated retina with connective tissue may form a mass within the vitreous cavity. The vitreous

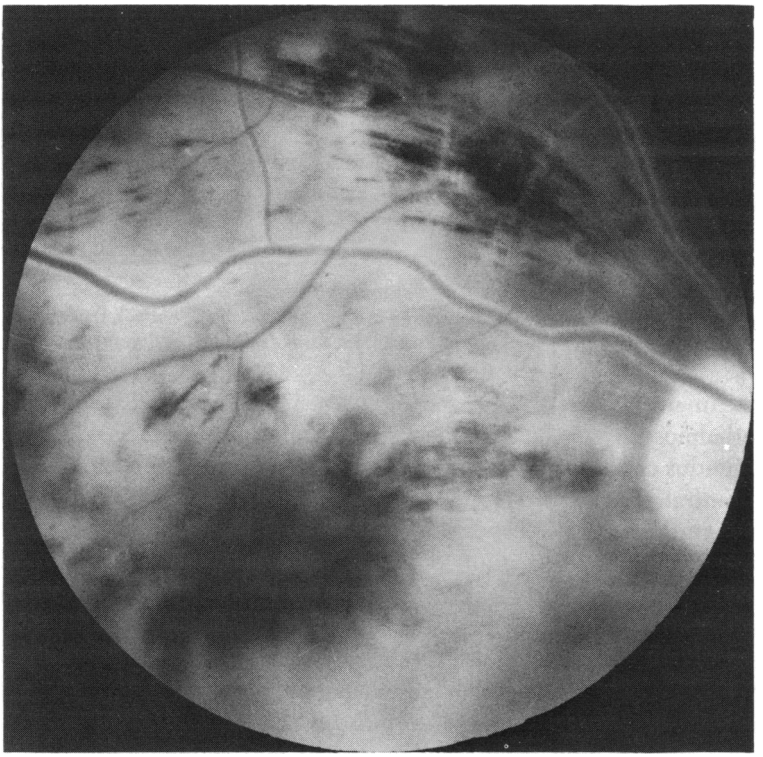

FIGURE 8
Fluorescein angiography of fundus shown in Fig 6, at 300 seconds after injection. Marked extravasation of fluorescein and tissue staining are seen.

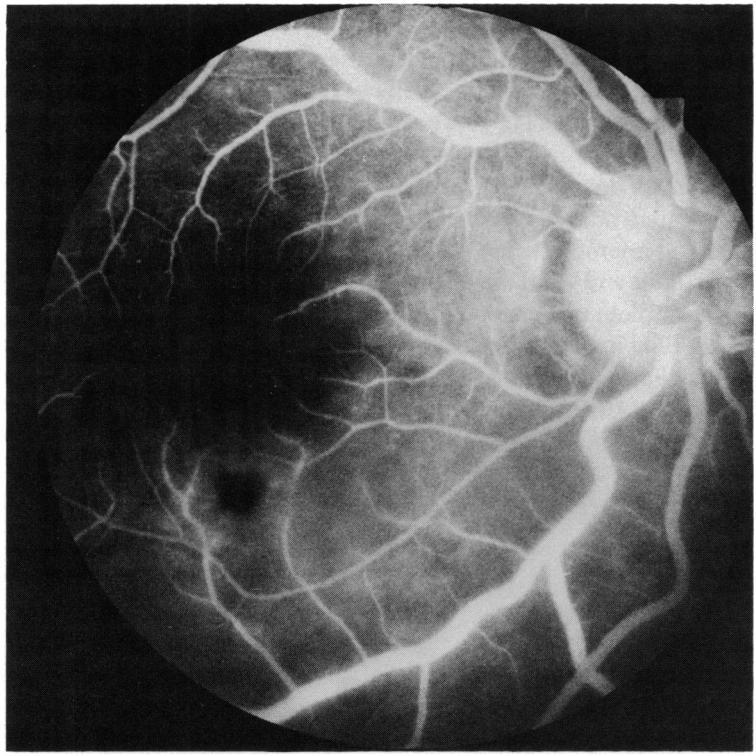

FIGURE 9
Fluorescein angiography of same patient as in Fig 6 at time of mild attack that occurred six months previously. Leakage of fluorescein from capillaries and veins is seen.

detachment is usually seen, and intensive vitreous opacity permitting no ophthalmoscopy is also a frequent finding. Besides these typical findings, the fundus changes may begin as papilledema,[100] papillitis, or occlusion of the central retinal arteries and veins. A case showing a type of tapetoretinal degeneration was also reported.[101]

Findings in fluorescein angiography were explored by Shimizu.[102] During the acute attack, occlusion of the capillary bed can be seen in association with the yellowish-white exudates and hemorrhages. Marked dilatation of the capillaries can be seen, particularly in the radial peripapillary capillaries. Diffuse dye leakage can be seen not only from the capillaries but also from larger vessels and also in the optic disc (Fig 7 and 8). In attacks of slight degree, where only venous engorgement and retinal edema are seen, diffuse dye leakage from the vessels is the constant finding (Fig 9). Even during the remission, such dye leakage from the vessels is found where

TABLE VI: CLINICAL TYPES OF OCULAR INVOLVEMENT*†

| TYPE | MALE | | FEMALE | | TOTAL | |
|---|---|---|---|---|---|---|
| | PATIENTS | EYES | PATIENTS | EYES | PATIENTS | EYES |
| Anterior segment type | 18 | 35 | 11 | 19 | 29 | 54 |
| Fundus type | 103 | 184 | 20 | 34 | 123 | 218 |
| Total | 121 | 219 | 31 | 53 | 152 | 272 |

*Cases were compiled from 1973 through 1977.
†From Namba et al.[98]

retinal edema is present. These changes are understood as a retinal angiopathy and are typical of this disease. Usually no particular changes are seen in the choroidal background fluorescence.

*Other ocular symptoms*

Episcleritis and keratitis of fascicular and filamentous type may also be seen.[61] Oniki[87] carried out careful follow-up of 63 cases of incomplete type that had not shown ocular changes, and found that ocular lesions developed in 11 cases in one to eight years; the initial ocular symptom was episcleritis in two cases, the iridocyclitis in four cases, and fundus changes in five cases. Subconjunctival hemorrhages, conjunctivitis, and extraocular muscle paralysis are also reported in the literature; the muscle paralysis is a sign of neuro-Behçet's syndrome.[68]

TYPES OF OCULAR AFFECTIONS

Many authors classified the ocular attacks into (1) anterior segment type, (2) fundus type, or (3) mixed or panophthalmic type, where both the anterior segment and the fundus are affected. A total of 152 cases (272 eyes) were

TABLE VII: TIME INTERVAL BETWEEN AFFECTIONS OF BOTH EYES*

| INTERVAL | MALE (128 CASES) | FEMALE (61 CASES) | TOTAL (189 CASES) |
|---|---|---|---|
| Within one month | 28 | 33 | 61 |
| In 6 months | 47 | 14 | 61 |
| In 1 year | 19 | 6 | 25 |
| In 2 years | 8 | 4 | 12 |
| In 3 years | 11 | 1 | 12 |
| In 4 years | 6 | 1 | 7 |
| In 5 years | 1 | | 1 |
| In 6 years | 3 | 1 | 4 |
| In 7 years | 2 | | 2 |
| More than 7 years | 3 | 1 | 4 |

*From Imai.[70]

observed for an average period of five years[98]; their sex distribution and the type of affection are shown in Table VI. During this observation period, in 29 cases (54 eyes, or about 20%) changes were confined only in the anterior segment; they may be called the anterior segment type. The remainder of the patients showed fundus changes, and they are fundus and mixed types. It is of interest to note that the fundus type is found in higher percentage in men than in women. In an analysis of 346 eyes, Asaoka[103] found that the ocular changes began as the anterior segment type in 50%, as the fundus type in about 34%, and as the panophthalmic type in about 9%; the eye symptoms were lacking in about 7%. Some cases of the anterior segment and fundus types eventually showed panophthalmic changes in the course of observation; finally, the types of affections were anterior segment type in 41.6%, fundus type in 15.9%, and panophthalmic type in 42.5%.

LATERALITY OF THE CHANGES

Both eyes are usually affected during a long period, but unilateral affection may be seen for a considerable period. Imai[70] conducted a follow-up study on 202 cases with ocular lesions and found 189 cases (93.6%) with bilateral affections. An analysis of the time interval between bilateral involvements is given in Table VII. In about 30% to 35%, both eyes were affected within a month; in another 30%, bilateral involvements occurred within six months, and in 13% within one year. In three years bilateral alterations developed in 90% of the patients, but there were cases where the interval between affections of both eyes was more than five years.

PATTERN OF OCULAR ATTACKS

*Duration and intervals*

Namba et al[98] followed up 38 cases for an average of three years and recorded 156 attacks involving the anterior segment and 178 attacks involving the fundus. The distribution of the duration of these attacks is shown in

TABLE VIII: COMPLICATIONS OF BEHÇET'S DISEASE IN 382 EYES (1973-1977)*

| | MALE (288 EYES) | | FEMALE (94 EYES) | | TOTAL | |
|---|---|---|---|---|---|---|
| | NO. OF EYES | (%) | NO. OF EYES | (%) | NO. OF EYES | (%) |
| Cataract | 110 | (38.2) | 26 | (27.7) | 136 | (35.6) |
| Optic atrophy | 51 | (17.7) | 7 | (7.4) | 58 | (15.2) |
| Macular degeneration | 40 | (13.9) | 11 | (11.7) | 51 | (13.4) |
| Glaucoma | 36 | (12.5) | 7 | (7.4) | 43 | (11.3) |
| Phthisis | 16 | (5.6) | 3 | (3.2) | 19 | (5.0) |
| Macular hole | 4 | (1.4) | 0 | | 4 | (1.0) |

*From Namba et al.[98]

Fig 10. The anterior segment attacks varied from 2 to 28 days, with an average of nine days. The fundus attacks lasted from 5 to 81 days, with an average of 23 days. The intervals between the attacks affecting the same person were studied irrespective of the laterality and types of involvement. Of 254 attacks, the interval varied from 2 to 1,082 days, giving an average of 96 days. The distribution of the interval is illustrated in Fig 11. Sometimes the interval was long, but once the attacks occurred, there was a tendency for the attack to recur at shorter intervals. This may have a relation with the meteorologic factors.

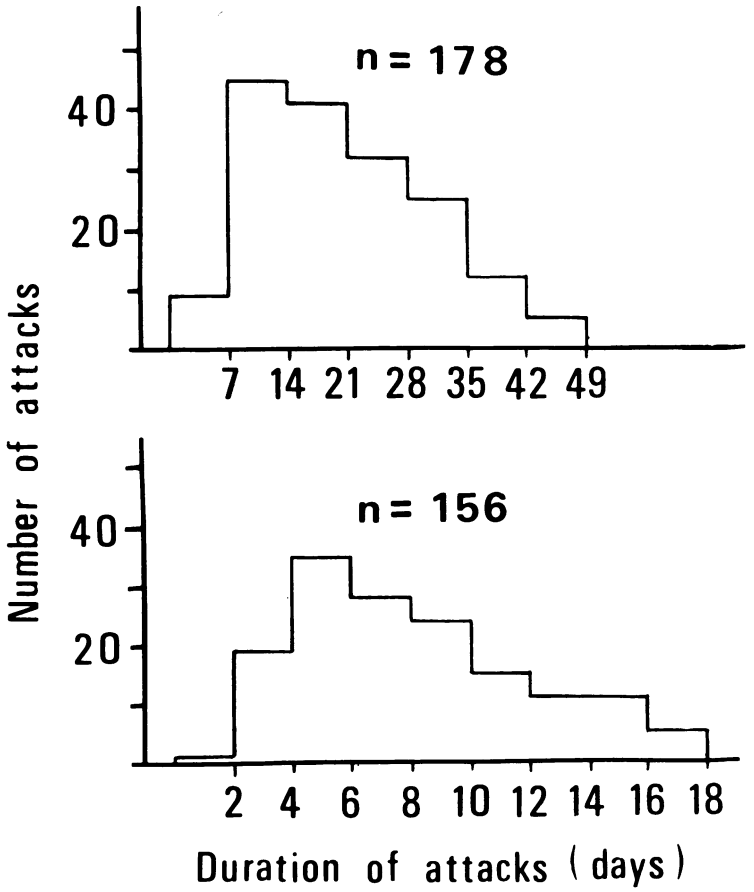


FIGURE 10
Distribution of durations of fundus attacks (top) and of anterior segment attacks (bottom) (from Namba et al[98]).

*Seasonal variation of attacks*

Oniki[87] showed for patients in the Kyushu district that the attacks are frequently seen during the winter from November to February. In a study on selected patients in the Tokyo area, attacks were also seen during the summer.[98] The frequency of attacks during the rainy season from late June to late July was almost 2.7 times the frequency during the remainder of the summer. This suggests meteorologic influence. A comparative study on the meteorologic data and ocular attacks[104] showed that the attacks occurred most frequently coinciding with sudden changes in the weather.

*Time of the day of attack*

Oniki[87] analyzed the time of day when the patients noted that the attack had occurred: evening in 34.1%, night in 20.7%, morning in 26.8%, daytime in 7.3%, and unknown in 11%. In the majority of cases, the attacks occurred between evening and the following morning.

OCULAR COMPLICATIONS

After repeated attacks, various ocular complications may develop, including cataract, glaucoma, macular degeneration, macular hole, optic atrophy, retinal detachment, and phthisis bulbi. During the five-year period from 1973 to 1977, 210 cases (382 eyes) of Behçet's disease were seen[98]; the frequency of complications and its sex distribution are given in Table VIII.

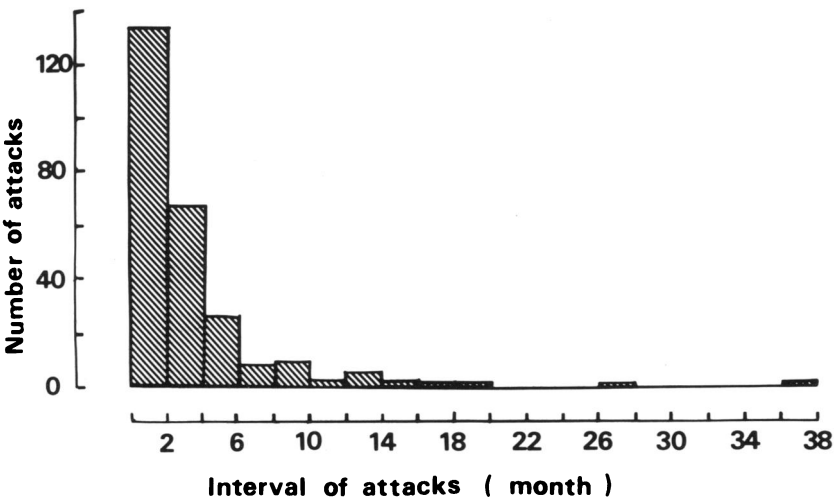


FIGURE 11
Distribution of intervals between attacks. Total of 254 attacks in 38 patients were analyzed (from Namba et al[98]).

Cataract was most frequent, occurring in 35.6%, followed by optic atrophy in 15.2%, macular degeneration in 13.4%, and glaucoma in 11.3%. These complications were much less frequent in females than in males, indicating again that the ocular involvement is less severe in females than in males. Cataract and glaucoma frequently develop in the anterior segment attacks, and the latter is largely due to pupillary seclusion and peripheral anterior synechiae. (Management of cataract will be discussed in the section on Treatment.) The time interval from the initial ocular attack to the development of complications varied depending on the severity of the attacks. In some cases severe complications appeared within a year, but in others several years were required.

VISUAL PROGNOSIS

It has been stated on many occasions that the visual prognosis of Behçet's disease is extremely poor and that the majority of patients become practically blind during the course of 3.5 years[105] or five years.[61,70,106] The main cause of visual deterioration following the attacks is fundus changes. An analysis of long-term follow-up of the visual acuity on 305 eyes of the fundus type and 54 eyes of the anterior segment type is illustrated in Fig 12. In the

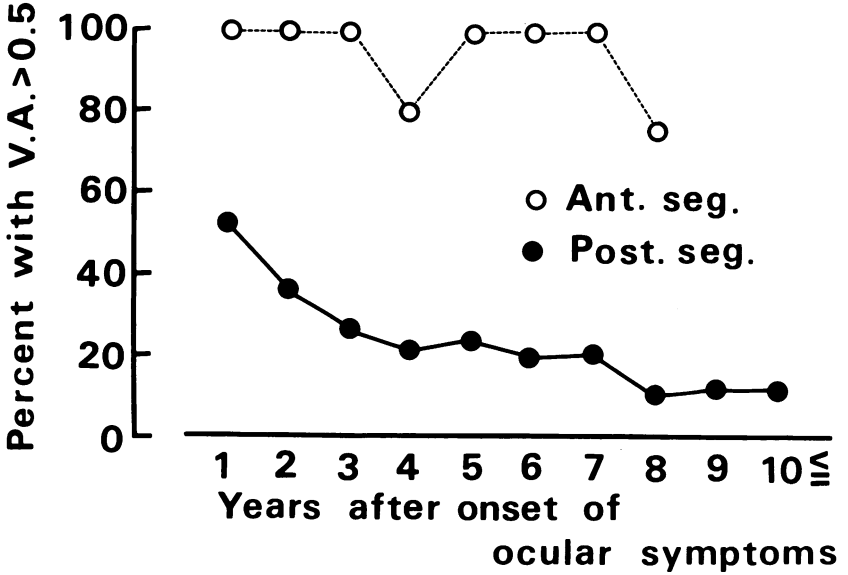


FIGURE 12

Percentage of patients having visual acuity (VA) better than 0.5 and its changes after onset of ocular symptoms. Analysis included 305 eyes with fundus type and 54 eyes with anterior segment type.

anterior segment type, a good visual acuity is retained for almost ten years, but in the fundus type only one quarter of the patients retained good visual acuity after five years of observation. In Fig 13, the visual acuities of the total and of the female patients are analyzed. In more than 50% of the total patients, the visual acuity deteriorated below 0.1 (20/200) in five years, but in female patients only 10% had vision this poor, and no further increase in the incidence was seen for more than ten years. One can conclude that the visual prognosis is better in females than in males. The clinical courses of the ocular changes reported from the Mediterranean countries[57,68,77,78,105] appear comparable to those of our patients, but the prognosis of the ocular changes reported from the United States[107-110] appears less severe than in our cases.

## OCULAR HISTOPATHOLOGY

The ocular histopathology of the recurrent hypopyon uveitis was reported by many authors: Before 1941, at least six cases were described in German literature: Gilbert (1921), Weve (1923), Hippel (1932), and Urbanek (1932) each reported one case, and Schmidt (1941) reported two cases. Three cases were reported in Japanese literature: Shigeta (1923), Nakayama

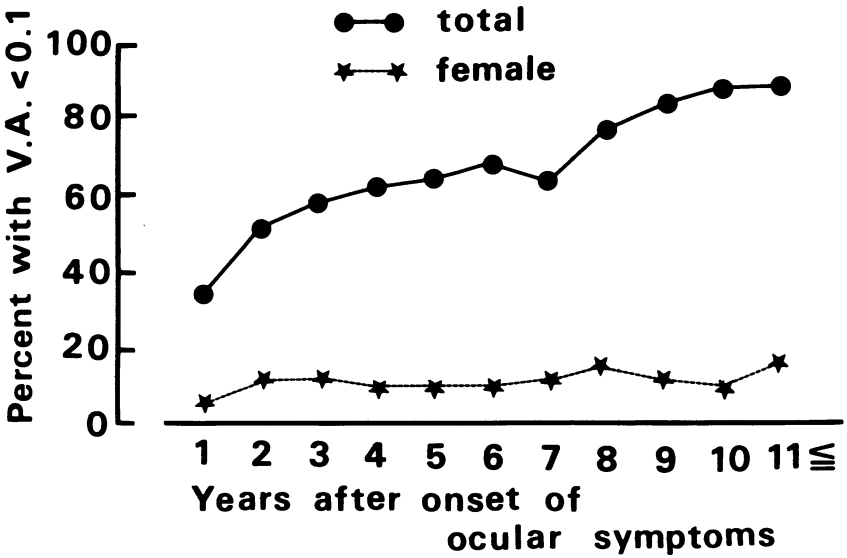


FIGURE 13
Percentage of patients with visual acuity (VA) less than 0.1 (20/200) and its changes after onset of ocular symptoms. Total of 152 patients (272 eyes) were analyzed, of which 31 patients (53 eyes) were females.

(1926), and Kawabata (1935). These were the cases of Behçet's disease. Furthermore, the pathology of one case, or of a few eyes, of this disease has been reported by many authors.[54,56,57,77,111-115] While alterations in various stages of the skin lesions, oral aphthae, and genital ulcers have been thoroughly explored, the ocular changes previously described are largely in advanced cases, since enucleation of the eye was possible only when patients suffered from extreme pain and had no useful vision because of complications. This rendered difficulty in obtaining an overall view on the ocular changes of this disease. Shikano reported pathology of more than 15 eyes in his series,[116-118] and Ikui et al[119,120] described nine cases from their own record and an additional seven cases collected from various Japanese investigators. Some of these eyes showed a stage of attack and others showed a stage of remission. In addition, some eyes in an early stage[121] and in less advanced stages[118] could be obtained after the accidental death of patients.

Many authors agree that the basic changes underlying various manifestations are inflammatory reactions in small vessels: infiltration of polymorphonuclear leucocytes, lymphocytes, and plasma cells in the vessel walls and thrombus formation are seen. Fibrinoid swelling of the connective tissue is also encountered. During passage of time, such inflammatory changes subside and slight diffuse fibrosis ensues. After recurrent attacks fibrotic changes are enhanced. In the ocular tissues, the histologic picture of the inflammatory changes is modified depending on the tissue affected.

### THE IRIS

During the attacks with conspicuous hypopyon, neutrophil leucocytes are seen abundantly not only in the anterior chamber but also in the iris stroma. In the early stage, the cells are almost exclusively neutrophil leucocytes, and only in the later stages do monocytes and lymphocytes appear. The leucocytes show little sign of leucocytoclasis. During the state of remission in the early stage, the iris shows little change, and slight cell infiltration is found around the iris vessels. Findings by electron microscopy are also not striking, and an increase of microvilli and vacuoles in the endothelial cells of the iris vessels, and of vacuoles in the perivascular cells, is encountered.[122] Thus, the acute attack of hypopyon leaves little tissue damage to the iris. After many recurrences of such attack, however, degeneration and atrophy of the iris occur and diffuse fibrosis can be seen.

### THE CILIARY BODY AND CHOROID

During the attacks, diffuse infiltration of leucocytes is seen, but during the remission, the ciliary body shows slight infiltration of lymphocytes. After

repeated attacks, plasma cells are also seen, and in advanced stages, atrophy and fibrosis may be found. In the choroid, diffuse swelling and thickening of the tissue with abundant leucocytes are found during the attack, but during the remission the tissue damage is not conspicuous and infiltration of lymphocytes is seen; after repeated attacks plasma cells are also encountered. In the latter stage, proliferation of collagen fibers are seen diffusely in the tissue. In the eyes that were in the state of phthisis, a marked thickening of the choroid is largely caused by increased tissue space, which occurred by loss of vitreous, and also by engorgement of the vessels and fibrosis.

### THE RETINA

While the tissue damage in the uvea after each attack appears slight, change in the retina is striking. During the attacks, severe angiitis is seen with marked infiltration of leucocytes in and around the vessel wall and also in the retinal tissue. Swelling of the endothelial cells is found and thrombus formation also occurs frequently. Veins and venules are often affected, but arteries are also affected. In severe inflammation, almost all infiltrating cells are neutrophil leucocytes. During remission, a few lymphocytes and plasma cells are found in and around the vessel walls. A striking finding in the retina is that localized disappearance of the visual cells and the inner nuclear layer occurs even in the eyes that are in less advanced stages; this is to an extent that cannot be interpreted as the sequelae of obstruction of the retinal vessels alone. The retina shows various degrees of degeneration and gliosis, depending on the damage inflicted by previous attacks. On the other hand, destruction of the pigment epithelium is not striking.

In advanced cases, the retina shows marked degeneration, and in many cases retinal detachment is found. Sometimes the detached retina forms a conglomerated mass in the vitreous cavity. The visual cells and ganglion cells almost completely disappear, and marked gliosis is found. Fibrosis of the vascular wall is intensive, and sometimes complete obliteration of vessels is seen. Even in these advanced cases, infiltration of lymphocytes is seen in the vessels.

By electron microscopy, Matsuda et al,[123] recently found tubular structures in the retina of two of nine eyes. They were an interwoven structure measuring 250 A and 60 A in the outer and inner diameters and were surrounded by limiting membrane. These structures were seen in the cytoplasmic space of the perivascular glial cells and occasionally in the fibroblasts of the vascular wall. Their ultrastructure appeared identical to those found in the systemic lupus erythematosus.

OTHER OCULAR TISSUES

The optic nerve often shows atrophy, which is considered secondary to the retinal changes in some cases, but in other cases optic nerve changes are caused by angiitis and cell infiltration within the optic nerve.[124] Some cell infiltration in the cornea and pericorneal and episcleral vessels was also reported.

NATURE OF THE OCULAR CHANGES

Nishimura[63] and Shikano[116,117] conducted serial histopathology of the erythema nodosum-type eruptions and pustules after prick test to show the sequence of pathologic changes. In the early stage, a slight infiltration of round cells around the small vessels and exudation from these vessels are seen in the subcutaneous tissue, and then fibrinoid swelling of the connective tissue fibers, increase in the infiltration of neutrophil leucocytes, and hemorrhages are seen. The leucocytes show little sign of leucocytoclasis and infiltrate diffusely in the tissue. After several days, tissue damage is repaired and, finally, diffuse fibrosis results. Comparison of these changes with the findings in the ocular histopathology led Shikano[118] to conclude that the ocular alterations are basically identical to those occurring in other organs. He further surmised that the ocular changes follow a similar sequence as described previously. Severe angiitis with intensive diffuse infiltration of neutrophil leucocyctes constitutes the attacks, which subside in the early stage without damaging much tissue in the uvea. In the retina, however, a severe localized damage occurs in the visual cells and other neural elements, although the retina appears to show little change by ophthalmoscopy. After many recurrences of such attack, destruction of the tissue occurs and diffuse fibrosis ensues. In the retina, complete disappearance of the neural elements and marked gliosis occur with retinal detachment.

## ETIOLOGY AND PATHOPHYSIOLOGY

Since the original report of Behçet, who claimed that elementary bodies were found in the tissues of oral and genital ulcers, possible viral etiology has been explored. Recently analysis of the histocompatibility antigens revealed strong linkage of this disease with HL-A-B5, and genetic contribution to the manifestation of this disease has been greatly elucidated. A sharp increase in the incidence of this disease in the early 1950s and an epidemiologic survey suggested the possibility of environmental factors in the etiology; searches along this line have also been conducted. Furthermore, many authors considered the roles of immunologic factors in the manifestations of this disease, and numerous studies have been carried out

on this subject. It was found that the patients show abnormalities not only in the immunologic system but also in various functional aspects, eg, serum enzymes, blood cells, fibrinolytic and blood clotting systems, and hormonal functions. In this section, studies on the etiology and pathophysiology will be reviewed.

### VIRUS ISOLATION

Successful virus isolation from the patients' material has been reported,[56,57,125-128] but negative results have also been reported by many investigators[31,32,77,107,108,112,129]: the viral etiology as proposed originally by Behçet[19-22] is not confirmed. Shishido[130] reviewed previous works on this aspect and reported works of his group indicating that all attempts of isolating a particular virus gave negative results. Electron microscopy of the tissues also failed to find evidence of virus infection.[122,130] Sugiura et al[131] reported that a complement fixation antibody to chlamydia was found at a significantly higher incidence in patients with Behçet's disease than in the control subjects. The tubular structures were found in the retina,[123] but it is not clear whether these structures represent the nucleocapsids of the paramyxovirus.[86] A possibility of slow virus infections has been tested, but so far no conclusive evidence has been obtained.[130] Since autoimmune reactions have been considered as a possible mechanism of manifestation, a possibility would remain that a certain virus infection may trigger such reactions. The epidemiologic surveys[11-13,89,90] showed that the patients are scattered, and no evidence of infection from patients to others was obtained.

### IMMUNOGENETICS

Through a series of immunogenetic studies on a large number of patients in Japan, Ohno et al[132-135] found that the incidence of the HL-A-B5 is significantly higher in patients than in the normal population (Table IX). In addition, high association of HL-A-BW51 subtype with Behçet's disease was found (Table X). A high incidence of HL-A-B5 in Behçet's disease has been confirmed in Japan[136-140] and was also found in Turkey,[141,142] Greece,[143] Tunisia,[144] Israel,[145] France,[146] Switzerland,[147] and England.[148] The geographic distribution of this disease appears to coincide with the geographic distribution of HL-A-B5 antigen.[135]

Ohno[135] recently correlated the incidence of HL-A-B5 with the various types of this disease; a high incidence, 69%, was found in the male complete type, followed by male patients with ocular involvement, female complete type, male incomplete type, and female patients with ocular involvement. The incidence in female patients without the ocular involve-

TABLE IX: INCIDENCE IN PERCENT OF HL-A ANTIGENS*

| HL-A ANTIGEN | CONTROL (130 CASES) | PATIENT (169 CASES) |
|---|---|---|
| A1 | 0 | 1 |
| A2 | 40 | 49 |
| A3 | 2 | 1 |
| A9 | 59 | 54 |
| A10 | 19 | 32† |
| A11 | 15 | 8 |
| A28 | 4 | 3 |
| AW19 | 18 | 15 |
| B5 | 31 | 62‡ |
| B7 | 12 | 10 |
| B8 | 0 | 1 |
| B12 | 13 | 9 |
| B13 | 2 | 1 |
| B14 | 0 | 0 |
| B15 | 18 | 16 |
| B17 | 1 | 1 |
| B18 | 0 | 0 |
| B27 | 0 | 1 |
| B40 | 32 | 30 |
| BW16 | 8 | 4 |
| BW21 | 0 | 0 |
| BW22 | 8 | 5 |
| BW35 | 13 | 13 |
| BW54 | 14 | 6 |

*From Ohno.[135]
†$\chi^2 = 6.12$; $P < 0.02$; relative risk = 2.0.
‡$\chi^2 = 27.87$; $P < 0.00001$; relative risk = 3.6.

ment was low. In an analysis of 144 patients with and 25 patients without the ocular involvement, HL-A-B5 was found in 63% in the former and in 52% in the latter group. However, HL-A-BW22 was found in only 2% in the former but in 50% in the latter group, and this difference was statistically significant. Thus, severe ocular involvement appears to be linked with the presence of HL-A-B5, and sparing of the ocular affections appears to be linked with the presence of HL-A-BW22.

TABLE X: INCIDENCE IN PERCENT OF HL-A-B5 SUBTYPES*

| | CONTROL (553 CASES) | PATIENT (40 CASES) | *P*-VALUE | RELATIVE RISK |
|---|---|---|---|---|
| HL-A-B5 | 38 | 73 | $P < 0.00003$ | 4.3 |
| HL-A-BW51 | 21 | 63 | $P < 0.00001$ | 6.1 |
| HL-A-BW52 | 14 | 10 | $P > 0.4$ | 0.67 |
| HL-A-BW53 | 0 | 0 | . . . | . . . |

*From Ohno.[135]

In studies of familial occurrence, all patients had HL-A-B5.[135,149] Ohno[135] carried out analysis on 14 families, 67 members, among whom 15 cases of Behçet's disease were found. All 15 patients had HL-A-B5, which was inherited from mothers in 13 cases. Furthermore, HL-A-typing of the parents revealed that 86% of mothers had HL-A-B5, whereas only 31% of fathers had this antigen. It was concluded that HL-A-B5 inherited from mothers plays an important role in the manifestation of this disease and that the relative risk in this case is as high as 39.7.

On the contrary, in nine patients in the United States[150] and in ten patients in the United Kingdom,[151] increase in HL-A-B5 frequency could not be demonstrated, and, instead, an increase in HL-A-A28 was suggested in the latter patient group. In 32 patients in England, HL-A-B5 was increased in male patients, but HL-A-B27 was found in significantly higher incidences in both sexes than in the normal control patients.[148]

### DETECTION OF RARE SUBSTANCES

Peripheral neuropathy is often found in the lower extremities, as evidenced by hypesthesia and reduction in the velocity of nerve conduction; in seven such cases, biopsy of the sural nerve revealed a reduction of myelinated nerve fibers.[152] A radiographic microanalysis showed high peaks of chlorine, phosphate, and copper in the axons. Similar high peaks were also found in the vascular endothelium in the nerve. Blood analysis of these patients showed a higher level of benzene hexachloride (BHC) and dichlordiphenyl-trichlor ethane (DDT) than in the control patients. A one-year follow-up of 17 patients with the radiographic microanalysis showed an increase in the copper content in the blood serum, which could be correlated with the ocular attacks.[153] In one enucleated eye, an extremely high content of copper, iron, zinc, and bromide was found in the aqueous humor and vitreous body. A high level of BHC in the patients' blood was also reported.[154]

### THE AQUEOUS HUMOR

The aqueous humor obtained at the time of the ocular attack was shown to have chemotactic activity to the polymorphonuclear leucocytes of rabbits, by the method of Boyden's chamber.[97] A follow-up study[155] revealed that the chemotactic activity increased two to three days before the onset of the attack when almost no leucocytes could be seen in the aqueous humor. The activity was then reduced two or three days after the appearance of hypopyon (Fig 14). Concurrent changes in the protein content in the aqueous humor were also found. Fractionation of the aqueous humor showed that the activity was found in the protein fraction and also in the prostaglandin

fraction.[156] Ultracentrifugation revealed that the activity peaks were at 14S, 6S, and 2S. Moreover, IgG and β-1 C/A globulin were found in the 6S and 2S fractions, respectively.[97] It was believed that accumulation of leucocytes in the anterior chamber might be induced by chemotactic factors, including those produced by complement. Prostaglandins E and F were found at a higher concentration in the aqueous humor of patients during the attack than in normal subjects[157]; the origin of prostaglandins could be leucocytes migrating into the anterior chamber. Both prostaglandins were shown to activate random leucocyte movement.[158]

Plasminogen was positive in 40% of the patients' aqueous humor, but it was negative in healthy persons.[159] However, plasmin and plasminogen activator were not detected. The plasminogen proactivator in the aqueous humor was significantly higher in patients than in the control group, and its

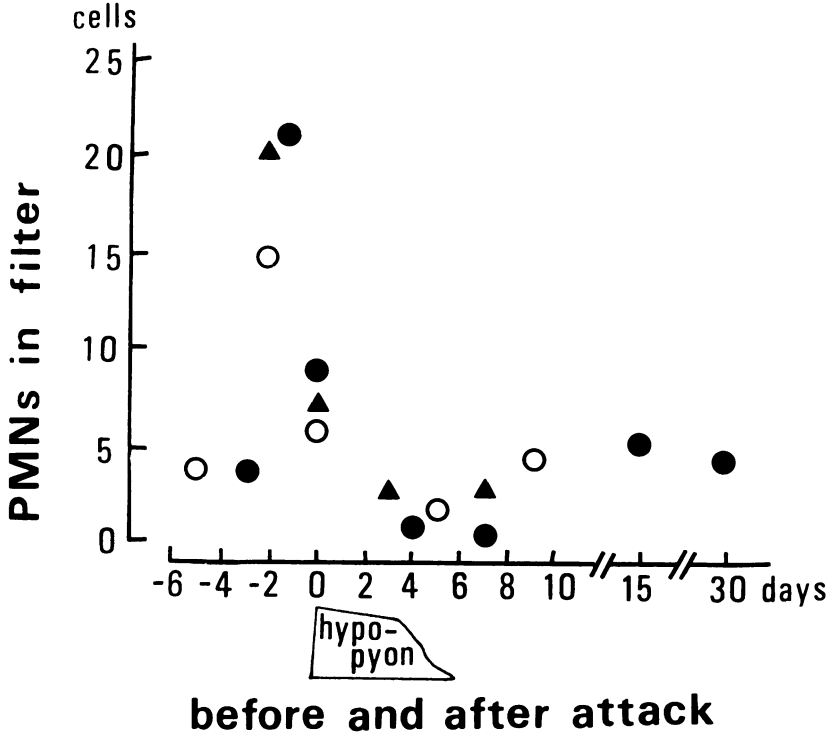


FIGURE 14

Changes in chemotactic activity in aqueous humor of patients. Ordinate is number of polymorphonuclear leucocytes (PMNs) of rabbits in millipore filter of the Boyden's chamber. The 0 day in abscissa indicates onset of hypopyon, extent of which is shown below abscissa. Each symbol represents each individual (from Masuda et al[155]).

aqueous-blood ratio was close to unity. This increase could be caused by transfer of blood proactivator across the damaged blood-aqueous barrier.

IMMUNOLOGICAL ASPECTS

The role of allergic reaction in the manifestation of this disease was first considered by Weve,[160] and later by other authors.[9,23,38,40,63] Since Oshima et al[161] demonstrated circulating autoantibody in patients against the oral mucous membrane, which increased shortly before and during the attacks of oral aphthae, immunologic events have been believed to play a significant role in the manifestation of various symptoms, and numerous studies have been carried out. Only those pertaining to the ocular changes will be reviewed.

*Serum and plasma analysis*

A high incidence of positive C-reactive protein,[8,63,161] high levels of mucoprotein[8,63,161] and $\alpha$-globulin,[87,100,161,162] and increase in $\gamma$-globulin, which decreases at the ocular attacks,[161,162] were noted. Analyses of immunoglobulin revealed that IgG increases during the attacks and decreases during the remission, IgA is raised in both stages, IgM does not show significant increase,[87,163,164] and IgD increases during the attacks.[165] No significant change in $\alpha_2$-macroglobulin was found in patients, but haptoglobin was raised and transferin was lowered.[87,163,164] The IgG level was reported to decrease during immunosuppressive treatment,[163] but no change was reported.[166]

The complement activity is usually higher in patients than in normal control subjects[166-168]; while the activity is within normal range or slightly high during remission, it is significantly elevated during the ocular attacks. A striking finding is that the complement titer shows a precipitous fall just before the attacks and it is raised within about three days to an abnormally high level; it is then decreased gradually as the inflammation subsides[87,167] (Fig 15). Measurements of the complement components[167] showed that the fall in the titer was caused by remarkable reduction in the C3 and also in the C4 and C2 components; the reduction is then believed to have occurred through the classic pathway. Almost all C3 protein had been converted to $\beta$-1A globulin. It was then inferred that a sudden consumption of the complement preceded the ocular attacks.

An increase of chemotactic factor to polymorphonuclear leucocytes was found in the patients' serum. A sucrose density gradient centrifugation revealed that the activity was in 13 to 15S and 9 to 10S; each of these fractions could be separated into two to three peaks by phosphocellulose column chromatography. In these fractions various amounts of IgG, IgM,

and their fragments, and also C3 components were detected.[169]

Immune complex was detected by $Cl_q$ radioimmunoassay method and platelet aggregation method in patients' serum in about 30% of the cases.[170]

*Cell-mediated immunity*

The subpopulation of the T cells and B cells in the peripheral blood shows no significant difference from that of the normal control subjects.[86,87,171]

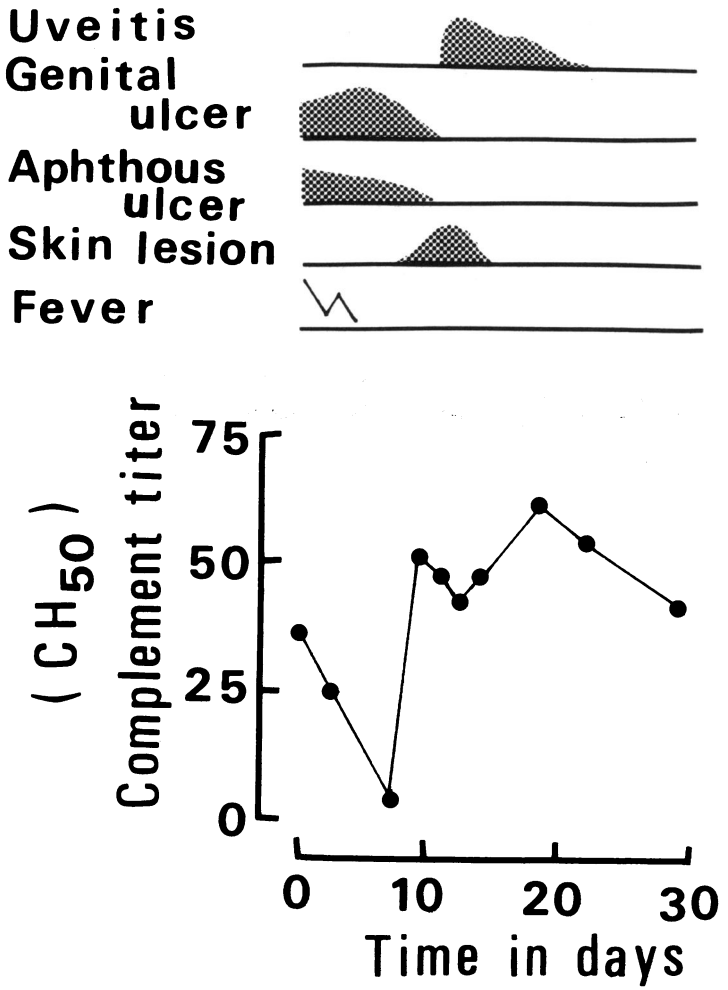


FIGURE 15

Changes in complement titer of serum and attacks. Time courses of grade changes of symptoms are illustrated (from Shimada et al[167]).

The responses of the former to phytohemagglutinin and of the latter to pokeweed mitogen did not differ from those of normal cells.[87,171] A follow-up of the subpopulation showed a reversal of the subpopulation during the ocular attacks in five of six patients.[172] The frequency of the IgG containing B cells was reported to be lower than in normal subjects,[71] but others reported no difference from the control subjects.[173] Role of cell-mediated immunity was tested by means of leucocyte migration inhibition test,[173-176] and significant inhibition was found with autologous aqueous humor obtained during the attack[174-176] but not with the aqueous humor during remission. Negative results were also reported,[173] but these could be caused by a difference in the stages at the time of aqueous sampling.

*Immunopathology*

The thrombus in the small vessels in the peripheral region of the choroid and pars plana of the ciliary body was stained with fluorescent antibody. The thrombus and the vessel wall were stained with anti-IgM and $\beta$1C/1A, but the specificity of this staining is uncertain.[86]

LEUCOCYTES

Leucocytosis in Behçet's disease has been noted by many authors since the review of France et al,[55] and this is a frequent finding. Leucocytosis is largely caused by increased neutrophil leucocytes. The leucocyte counts conducted repeatedly in selected patients were analyzed[98] in connection with the ocular attacks, and the results are shown in Fig 16. A sharp increase in the leucocyte counts was seen before the attacks; this increase was maintained for about two weeks after the onset and then it decreased. The activity of leucocytes as tested by nitroblue tetrazolium reduction was shown to increase significantly during the attack.[87,173,177] Furthermore, the chemotactic activity of the neutrophils was shown to be higher in patients than in normal subjects.[178] The lysosomes of the neutrophil leucocytes were stained with acridine orange; the distribution of the fluorescence intensity had a single peak in the weak fluorescence range in normal subjects, but it showed double peaks in patients.[179] The peak in the stronger fluorescence range increased significantly during the attacks. In addition, the microviscosity and flow activation energy of the cell membrane of the neutrophils were found to be augmented in patients but not in normal subjects.[179] These findings suggest that some functional abnormality is present in the neutrophil leucocytes of the patients.

ERYTHROCYTES

I blood type was tested in 54 patients, 35 normal subjects and 19 newborn

babies.[180] All normal subjects were I-positive and all babies were I-negative. On the other hand, I-negative was found in 21 patients (38.9%). Electrophoresis of the erythrocytes was carried out after pretreatment with neuraminidase and application of phytohemagglutinin.[86] The relationship between the percent change of the cell mobility and the concentration of phytohemagglutinin showed biphasic changes in patients, but such changes could not be seen in normal subjects. It was believed that the glycoprotein chain of the surface membrane of the erythrocytes showed some abnormality and that changes in the surface electric charge may play a role in intravascular erythrocyte agglutination in this disease. The activities of pyruvic acid kinase and glyceraldehyde-3-phosphate dehydrogenase were found to be higher in patients than in normal control subjects.[181]

FIBRINOLYTIC ACTIVITY

The fibrinolytic activity was studied in 35 patients[159,182]: plasmin, plasminogen activator, and fibrin degradation products were detected at a significantly higher frequency in the blood of the patients than in normal control subjects and in patients with other types of uveitis. Serial daily determinations in selected cases showed that the fibrinolytic activity tended to be reduced two to three days before the ocular attacks, was raised five to six days later, and then returned gradually to its previous level. The rate of detection of the fibrin degradation products was higher during the

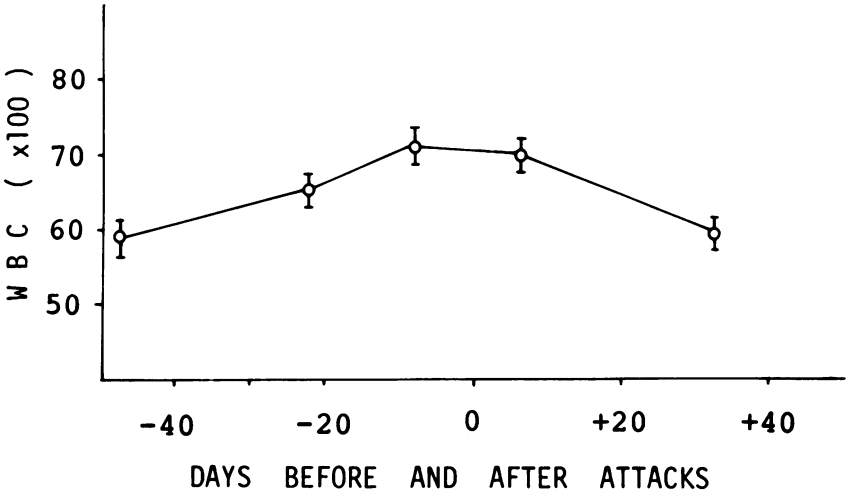


FIGURE 16

Changes in leucocyte counts before and after ocular attack. Total of 135 attacks in 38 patients were analyzed. Ordinate: No. of leucocytes (WBC) in $mm^3$. Day 0 in abscissa is day of onset of attacks (from Namba et al[98]).

attacks than in remission. A decrease in the fibrinolytic activity was also reported to occur at attacks, particularly in patients with thrombophlebitis.[95]

BLOOD CLOTTING SYSTEM

The platelet count, bleeding time, coagulation time, and prothrombin time remained within normal range, and no significant fluctuation could be found during the attack and remission.[183] However, the partial thromboplastin time was in the lower limit of the normal range, and it was prolonged during the attack and returned to the lower level during the remission. Fibrinogen and factor VIII were reported to be at a higher level than in normal subjects.[95] Platelet aggregation by adenosine diphosphate (ADP) was significantly elevated over normal values.[184] Fluctuation in the ADP aggregation appeared to parallel with the exacerbation and remission of the symptoms.

SERUM BIOCHEMISTRY

The activities of acid phosphatase, β-glucuronidase, and protase inhibitor

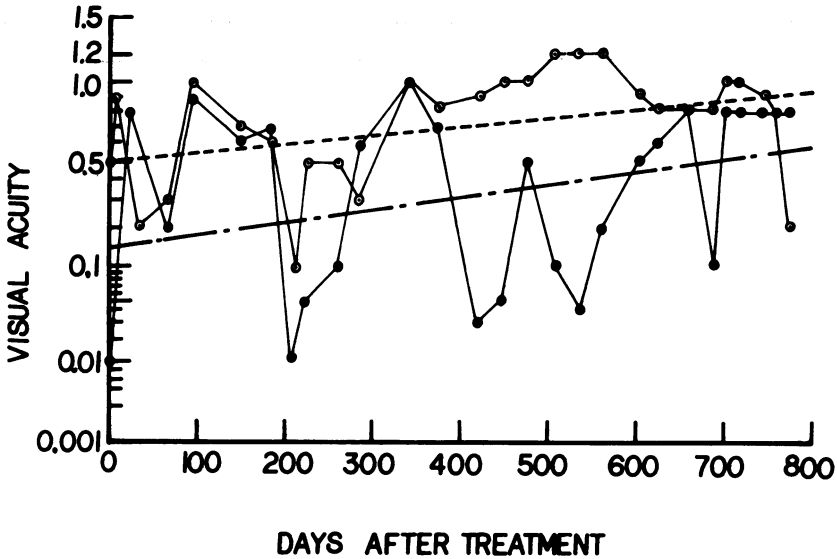


FIGURE 17

Example of logarithmic expression of visual acuity changes and of fitting regression lines. Results on right eye (○, - - - -) and left eye (●, -·-·-) of 25-year-old man treated with cyclophosphamide are shown. Visual acuity in ordinate is expressed in $-\log \log (V_{max}/V)$, where V is visual acuity expressed in conventional decimal fraction and $V_{max}$ is 4.0. Lines are regression lines fitted by a least-square method (from Hijikata and Masuda[209]).

are elevated in the serum of the patients, and follow-up studies showed that the activity becomes higher at the time of the attacks.[185,186] It is probable that the increased activity in the lysosomal enzymes is caused by release from polymorphonuclear leucocytes. Among many factors of release, presence of immune complex and heat-labile labilizing factor in the serum was considered. The activity of the latter factor was found in the albumin fraction.[186]

PITUITARY-ADRENAL FUNCTION

Studies on 12 patients revealed that after cold stress test, increase in the plasma cortisol was significantly less in patients than in the normal control subjects.[187] In follow-up studies of the individual cases, it was shown that immediately before ocular exacerbation, the plasma cortisol level fell abruptly. Furthermore, diurnal variation of plasma cortisol level was irregular in many patients, suggesting presence of pituitary-adrenal dysfunction.

AUTONOMIC FUNCTION

Methacholine chloride tests revealed that many patients showed choliner gic-type response, particularly at the time of attacks,[188] and the blood pressure was rather low in the majority of cases. Furthermore, a recording of the polygram during sleep showed that in patients with Behçet's disease, the latency of the stage rapid eye movement (REM) was shortened and the percentage REM (the percentge of the REM stage duration to the total sleep stages) was increased. In addition, an atypical pattern was seen in the REM stage.[189] These results suggest that the attacks of Behçet's disease tend to appear under the condition of cholinergic state. Frequent attacks during the evening and night[87] are in keeping with these findings.

EXPERIMENTAL MODEL

Ishikawa and others[190,191] fed miniature pigs of Pitman-Moor strain various doses of the mixture, ie, BHC (1 mg/kg), DDT (1 mg/kg), organic phosphorus (Sumition 4 mg/kg, Sumitomo Kagaku), and copper (2 mg/kg). They found development of folliculitis, erythema nodosum-like eruption around the anus in five months, genital ulcers in nine months, and oral aphthae in ten months. Furthermore, radiographic microanalysis of the leucocytes and vascular endothelial cells of the genital ulcers revealed high peaks of chlorine, phosphorus, copper, and sulfur, in a similar pattern as was found in human material.[152,153] The same findings were also obtained from the cutaneous and oral lesions. Resemblance of the symptoms and the results of radiographic microanalysis led them to consider that this animal may be used as an experimental model of Behçet's disease. In the eye, con-

TABLE XI: USE OF CORTICOSTEROIDS AND VISUAL PROGNOSIS*

| METHODS OF ADMINISTRATION | TOTAL NO. OF EYES | VISUAL ACUITY LESS THAN 0.01 | 0.02-0.4 | BETTER THAN 0.5 |
|---|---|---|---|---|
| Long-term systemic | 136 | 63 (46.3)† | 48 (35.3) | 25 (18.4) |
| Systemic only at attacks | 344 | 105 (30.5) | 127 (36.9) | 112 (32.6) |
| Instillation, subconjunctival injection | 258 | 43 (16.7) | 108 (41.9) | 107 (41.5) |
| No corticosteroid | 90 | 14 (15.6) | 54 (60.0) | 22 (24.4) |

*From Urayama.[71]
†No. of eyes (percent) is shown.

junctivitis was seen but no uveitis was found, perhaps owing to the relatively short time-period of feeding. It was suggested that one of the factors in the manifestation of Behçet's disease might be chronic exposure to multiple pollutants of the environment. In fact, the epidemiologic survey on Japanese population living elsewhere[92] points to such possibility.

## TREATMENT

Various modalities have been tried for the treatment of this disease: removal of focal infection, antibiotics, vaccines, γ-globulin, nonspecific desensitization, vitamins, and anticoagulants.[77,192] Their therapeutic effects were, however, disappointing. In the 1950s, corticosteroids were introduced, but opinions on their efficacy were contradictory. A retrospective study on 414 patients who had been under long-term follow-up clearly indicated that use of systemic corticosteroids resulted in poor visual prognosis[71] (Table XI), and this was confirmed by many others.[86,87] Since the

TABLE XII: ANALYSIS OF VISUAL ACUITY CHANGES*

| GROUPS | NO. OF DATA | RATE CONSTANT† $\times 10^{-4}$/day | $\sigma^2$ w‡ $\times 10^{-8}$/day$^2$ | $\sigma^2$ b§ $\times 10^{-8}$/day$^2$ | MEAN RESIDUALS// $\times 10^{-2}$ |
|---|---|---|---|---|---|
| Cyclophosphamide | 43 | 0.50 | 0.60 | 3.96 | 0.67 |
| Colchicine | 18 | 0.10 | 0.93 | 2.80 | 0.81 |
| Cyclophosphamide and colchicine | 38 | 0.66 | 0.97 | 4.32 | 0.79 |
| Control | 69 | −2.11 | 1.32 | 9.23 | 1.54 |

*From Hijikata and Masuda.[209]
†Mean slopes of regression lines fitted to chart such as shown in Fig 17.
‡Mean variance of rate constant within data.
§Mean variance of rate constant among data.
//Mean residuals divided by number of measurement points, which were calculated in fitting regression line by a least-square method. Residuals represent degree of visual acuity fluctuations.

cause of Behçet's disease is unknown, the immediate objective in the treatment from the ophthalmologic point of view has been to reduce the frequency and severity of the attacks and thereby prevent irreversible visual deterioration. Recently various immunosuppressants were found to be of some value for this purpose. Clinical trials of other drugs have also been undertaken.

IMMUNOSUPPRESSANTS AND COLCHICINE

Since immunologic processes are believed to be in the chain of events in the manifestation of this disease, various immunosuppressive agents have been tried. Among many agents, azathioprine,[193-198] chlorambucil,[199-205] and cyclophosphamide[71,86,87,206-209] were reported to have favorable therapeutic effects. Because of their toxicity, however, only cyclophosphamide gained popularity in the field of ophthalmology. Since the chemotactic mobility of leucocytes is enhanced at the time of attack, colchicine was introduced to suppress the mobility[178] and was found to be effective.[178,209,210]

An extreme variability of the symptoms during the attacks, including the visual acuity, of the duration of the attacks, and of the intervals of the attacks makes evaluation of the therapeutic effects of the agents difficult. Therefore, the trend of the visual acuity changes over a long period of observation was believed to be a better index for the evaluation than other methods of symptom grading or simple comparison of the visual acuities before and after treatment.[207,209] Hijikata et al[209] used a logarithmic function of the visual acuity to illustrate the time course of its changes without dependence on the initial visual acuity and found that a regression line could be fitted to the time course (Fig 17). On the basis of this technique, they evaluated the therapeutic effects in a total of 168 trials consisting of four groups of patients with the fundus-type affections who received the following medications: (1) cyclophosphamide, 50 to 100 mg/day, (2) colchicine 0.5 to 1.0 mg/day, (3) cyclophosphamide, 50 mg/day, and colchicine, 0.5 mg/day, and (4) patients compiled retrospectively from the records before introduction of cyclophosphamide, who had been under nonsteroidal anti-inflammatory agents, corticosteroids, and nonspecific desensitization agents. The fourth group constituted the control to the other three groups. The slopes of the regression lines were compared among the four groups (Table XII); the three drug groups had positive average slopes, whereas the fourth control group had a negative slope. Furthermore, the residuals calculated by fitting the regression line by a least-square method were also compared: it was significantly greater in the control group than in the other three groups. Among the three drug

groups, these values showed no significant differences. The residuals represent the fluctuation of the visual acuity and were positively correlated with the mean number of attacks per year. Thus, the use of cyclophosphamide, colchicine, or both could suppress the ocular attacks and helped patients maintain the visual acuity.

These drugs are cytotoxic and affect particularly the reproductive organs. An analysis[212] of the sperm in patients showed that all patients who received cyclophosphamide exceeding a total dose of 5.6 gm had azoospermia. A biopsy of the testis in a patient who received a total dose of 57.2 gm of cyclophosphamide and who had azoospermia revealed disappearance of spermatogenesis in some tubuli, but some tubuli appeared normal. In female patients, amenorrhea has been found frequently. At our clinic, gastrointestinal problems have been seen in some cases and hair loss was observed on rare occasions. In a survey[213] on the side effects of colchicine, oligospermia was found in about 10% and amenorrhea or dysmenorrhea was found in about 20%. In addition, nausea, gastralgia, and diarrhea were found in a few, and general malaise and hair loss were seen rarely. With the present doses of these drugs, no serious side effects have been reported, with the exception of the affection to the reproductive organs.

### OTHER DRUGS

Recently Levamisol (L-(-)-2,3,5,6-tetrahydro-6-phenylimidazo [2,1-b] thiazole hydrochloride) (Janssen Pharmaceutica, obtained from Kyowa Hakko Co), which is considered to enhance immunologic capacity, has been tried on a small number of patients.[214,215] The therapeutic efficacy of this drug is to be evaluated. In view of the behavior of the fibrinolytic system during the attacks, antiplasmin agents were also tried on a small number of patients.[215] On the basis of the findings of radiographic microanalysis, a chronic intoxication by substances including chlorine was suspected and, therefore, cholestylamine was tried. In addition, atropine (0.3 to 0.5 mg/day) was given since the ocular attacks were believed to occur frequently in a cholinergic state.[152] The efficacy of this method is to be proved.

### OUR CURRENT MEDICATIONS

Many ophthalmologists agree on the basic principle of medications for the ocular involvement of Behçet's disease. In the anterior segment type, only topical medications are given, unless the patients show severe systemic manifestations. Usually instillations of atropine or homatropine are done when the inflammation is deemed to require these drugs. Corticosteroid may also be instilled in severe inflammation, and subconjunctival injection

of corticosteroid may be done at a minimal dose when the iridocyclitis is severe, exhibiting a marked opacity in the anterior vitreous. However, corticosteroid must be curtailed as the inflammation subsides, and care must be taken to minimize its dose.

In the fundus and mixed types, systemic medications are given in addition to the topical therapy. The daily doses are 50 to 100 mg for cyclophosphamide and 0.5 to 1.0 mg for cholchicine. When both drugs are used in combination, cyclophosphamide, 50 mg/day, and cholchicine, 0.5 mg/day, are given. During treatment, leucocyte counts are obtained at every visit, which is usually at one-week to one-month intervals. In view of the behavior of leucocytes at the time of attacks, the drug dose is controlled so that the leucocyte counts are maintained between 4,000 and 6,000/mm.$^3$ When the leucocyte counts are less than this level, the dose should be reduced. In addition, nonsteroidal anti-inflammatory agents and vitamins may also be used, but systemic corticosteroid should be avoided.

With the present doses of cyclophosphamide and colchicine, no serious side effects have been recorded, but the patients must be informed of the side effects to the reproductive organs and be allowed to make their own decision. Without the consent of the patients, these drugs should not be used.

## SURGERY OF COMPLICATED CATARACT

The complicated cataract is the most frequent complication, and surgical removal may be indicated when visual improvement is expected. However, the choice of the time of surgery must be carefully exercised; after close follow-up of patients, the time with likelihood of long-lasting remission must be chosen. With this precaution, Mimura[217] operated on 74 eyes, and in our record 39 eyes of 27 patients were operated on with the follow-up period of at least six months. In both records, the results were similar. In our own records, the patients were aged 22 to 67 years. The intracapsular extraction was performed in 36 eyes, mostly with sector iridectomy and with conventional extracapsular extraction in one eye and aspiration with two canulas in two eyes. Shortly after surgery visual improvement was seen in about 85%, but 25% of the cases showed subsequent deterioration, and improvement in the final visual acuity was obtained in about 60%. Early postoperative complications included anterior chamber hemorrhage in five eyes and recurrence of hypopyon within one week in one eye. In ten eyes the postoperative inflammation was more intense than in the conventional intracapsular extraction of senile cataract. Otherwise, the immediate postoperative course was uneventful. A comparison of the attack frequencies was carried out for the equal preoperative and postoperative periods for

each patient, ranging from seven months to two years. In one case apparent postoperative increase was seen, but no particular change was noted in the majority of cases.

SUMMARY

The problems of Behçet's disease in Japan have been reviewed with particular emphasis on the ophthalmologic aspects: the historical background for the Japanese works, diagnostic criteria, epidemiology, some statistics, ocular symptomatology, ocular histopathology, etiology, pathophysiology, and treatment. Behçet's disease is the most frequent entity in endogenous uveitis in Japan. Patients are found throughout the country, and the prevalence rate averages seven to eight per 100,000 population: the rate is higher in the northern than in the southern districts. The diagnosis is made on the basis of a combination of clinical symptoms that are divided into the major and minor criteria symptoms. The major criteria comprise the ocular involvement, aphthous ulcers of the oral mucous membrane, genital ulcers, and skin lesions. These symptoms recur often as attacks and the disease follows a chronic course.

The ocular involvement is found in 83% to 95% in males and 67% to 73% in females; the male to female ratio in the number of patients is 1.78. Both eyes are affected in 90% of patients. The ocular involvement is classified into the anterior segment type and the fundus and panophthalmic types. The anterior segment type shows serous iridocyclitis with the classic type of hypopyon appearing in about 12% of the attacks. This type is found in about 20%, more often in females than in males, and the visual prognosis is more favorable than in the fundus and panophthalmic types. In the latter two types, attacks of retinal angiitis resulting in intensive retinal edema, yellowish-white exudate, and hemorrhages recur particularly in the macular region, and the visual prognosis is poor. More than 50% of male patients lose visual acuity to less than 0.1 in five years, but this is the case in only 10% of female patients. Consequently, Behçet's disease is the cause of blindness in about 12% of acquired blindness in adults. The ocular histopathology during the attack is characterized by severe angiitis with intensive infiltration of neutrophil leucocytes largely in the uveal tract and the retina; the latter is severely affected and loss of visual cells and other neural elements results. The etiology of this disease still remains unknown, but genetic predisposition is suggested since this disease is strongly linked with HL-A-B5. Environmental factors are also considered. Various abnormalities are found in the blood chemistry, blood cells (particularly in neutrophil leucocytes), immunologic mechanism, fibrinolytic and blood

clotting system, and hormonal system. Chemotactic factors are found in the aqueous humor. These changes are particularly enhanced just before and during the ocular attacks.

Systemic corticosteroids are deleterious to the visual prognosis, but cyclophosphamide and colchicine appear to suppress attacks and help patients maintain the visual acuity. However, these drugs are toxic, particularly to the reproductive organs, and the patients must be informed of this side effect and be allowed to make a decision before they are used.

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